

Rooke, A.  
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FILE 'REGISTRY' ENTERED AT 15:03:15 ON 03 MAR 2005  
L1 16 S REDEDEIEW/SQSP

Seq.  
Claim 27

FILE 'CAPLUS' ENTERED AT 15:03:36 ON 03 MAR 2005  
L2 21 S L1

L2 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
ED Entered STN: 19 Nov 2004  
ACCESSION NUMBER: 2004:995647 CAPLUS  
DOCUMENT NUMBER: 141:421046  
TITLE: Protein and cDNA sequences of the novel human tumor  
suppressor genes ASPP (apoptosis stimulating proteins  
of p53) and therapeutic use  
INVENTOR(S): Lu, Xin  
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA  
SOURCE: U.S. Pat. Appl. Publ., 81 pp., Cont.-in-part of U.S.  
Ser. No. 343,649.  
CODEN: USXXCO  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 2  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004228866	A1	20041118	US 2004-819095	20040405
WO 2002012325	A2	20020214	WO 2001-GB3524	20010806
WO 2002012325	A3	20030306		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004053262	A1	20040318	US 2003-343649	20030904
PRIORITY APPLN. INFO.:			GB 2000-19018	A 20000804
			GB 2000-29996	A 20001208
			GB 2001-12890	A 20010526
			WO 2001-GB3524	W 20010806
			US 2003-343649	A2 20030904

AB The disclosure relates to the identification of a new member of a family  
of tumor suppressor genes (apoptosis stimulating proteins of p53, ASPP's)  
which encode polypeptides capable of modulating the activity of p53, p63  
and p73, and polypeptides capable of modulating the activity of a tumor  
suppressor polypeptide.

IT 795109-26-1P

RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic  
use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(amino acid sequence; protein and cDNA sequences of novel human tumor  
suppressor genes ASPP (apoptosis stimulating proteins of p53) and  
therapeutic use)

L2 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 17 Nov 2004  
 ACCESSION NUMBER: 2004:979661 CAPLUS  
 DOCUMENT NUMBER: 142:18208  
 TITLE: The status, quality, and expansion of the NIH full-length cDNA project: The mammalian gene collection (MGC)  
 AUTHOR(S): Gerhard, Daniela S.; Wagner, Lukas; Feingold, Elise A.; Shenmen, Carolyn M.; Grouse, Lynette H.; Schuler, Greg; Klein, Steven L.; Old, Susan; Rasooly, Rebekah; Good, Peter; Guyer, Mark; Peck, Allicon M.; Derge, Jeffery G.; Lipman, David; Collins, Francis S.  
 CORPORATE SOURCE: The MGC Project Team, NIH, USA  
 SOURCE: Genome Research (2004), 14(10b), 2121-2127  
 CODEN: GEREFS; ISSN: 1088-9051  
 PUBLISHER: Cold Spring Harbor Laboratory Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The National Institutes of Health's Mammalian Gene Collection (MGC) project was designed to generate and sequence a publicly accessible cDNA resource containing a complete open reading frame (ORF) for every human and mouse gene. The project initially used a random strategy to select clones from a large number of cDNA libraries from diverse tissues. Candidate clones

were chosen based on 5'-EST sequences, and then fully sequenced to high accuracy and analyzed by algorithms developed for this project. Currently, more than 11,000 human and 10,000 mouse genes are represented in MGC by at least one clone with a full ORF. The random selection approach is now reaching a saturation point, and a transition to protocols targeted at the missing transcripts is now required to complete the mouse and human collections. Comparison of the sequence of the MGC clones to reference genome sequences reveals that most cDNA clones are of very high sequence quality, although it is likely that some cDNAs may carry missense variants as a consequence of exptl. artifact, such as PCR, cloning, or reverse transcriptase errors. Recently, a rat cDNA component was added to the project, and ongoing frog (*Xenopus*) and zebrafish (*Danio*) cDNA projects were expanded to take advantage of the high-throughput MGC pipeline. The sequence data for the full-length clones from this study have been submitted to GenBank/EMBL/DDBJ under accession nos.

BC000001-BC077073. [This abstr record is one of 39 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 606804-01-7, GenBank AAH58918  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (amino acid sequence; status, quality, and expansion of the NIH full-length cDNA project and mammalian gene collection (MGC))

L2 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 10 Sep 2004  
 ACCESSION NUMBER: 2004:740438 CAPLUS  
 DOCUMENT NUMBER: 141:258758  
 TITLE: Human nucleic acid and encoded protein sequences overexpressed in prostatic carcinomas  
 INVENTOR(S): Hinzmann, Bernd; Dahl, Edgar; Rosenthal, Andre; Hermann, Klaus; Pilarsky, Christian; Specht, Thomas; Schmitt, Armin; Beckmann, Georg; Bruemmendorf, Thomas;

Kinnemann, Henrik; Roepcke, Stefan; Li, Xinzong;  
 Staub, Eike  
 PATENT ASSIGNEE(S): Germany  
 SOURCE: PCT Int. Appl., 1607 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: German  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004076614	A2	20040910	WO 2004-DE433	20040222
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ, MZ, NA, NI, NI, NO				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10309985	A1	20040930	DE 2003-10309985	20030227
DE 10322134	A1	20041223	DE 2003-10322134	20030514
PRIORITY APPLN. INFO.:			DE 2003-10309985	A 20030227
			DE 2003-10322134	A 20030514

AB The invention relates to novel human nucleic acid sequences obtained from prostatic carcinomas and to proteins and peptides coded by said sequences. Over-expression of the nucleic acids was identified by chip anal. and quant. PCR. Differential expression of CD24 is demonstrated by GeneChip technol. and by immunohistochem. These nucleic acids and proteins may be used for the diagnosis and/or treatment of prostatic cancer, in screening assays for modulators of gene expression and/or protein activity, and for the design of antisense oligonucleotides, siRNAs, ribozymes, peptides, aptamers, and antibodies.

IT 753036-25-8

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (amino acid sequence; human nucleic acid and encoded protein sequences obtained from prostatic carcinomas)

L2 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 04 Jun 2004

ACCESSION NUMBER: 2004:449884 CAPLUS

DOCUMENT NUMBER: 140:420388

TITLE: Binary prediction tree modeling with many predictors and its uses in clinical and genomic applications

INVENTOR(S): Nevins, Joseph R.; West, Mike; Huang, Andrew T.

PATENT ASSIGNEE(S): Duke University, USA

SOURCE: PCT Int. Appl., 886 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 5

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004038376	A2	20040506	WO 2003-XB33946	20031024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2004038376	A2	20040506	WO 2003-US33946	20031024
WO 2004038376	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:				
			US 2002-420729P	P 20021024
			US 2002-421062P	P 20021025
			US 2002-421102P	P 20021025
			US 2002-424701P	P 20021108
			US 2002-424715P	P 20021108
			US 2002-424718P	P 20021108
			US 2002-425256P	P 20021112
			US 2003-448461P	P 20030221
			US 2003-448462P	P 20030221
			US 2003-457877P	P 20030327
			US 2003-458373P	P 20030331
			WO 2003-US33946	A 20031024

AB The statistical anal. described and claimed is a predictive statistical tree model that overcomes several problems observed in prior statistical models and regression analyses, while ensuring greater accuracy and predictive capabilities. Although the claimed use of the predictive statistical tree model described herein is directed to the prediction of a disease in individuals, the claimed model can be used for a variety of applications including the prediction of disease states, susceptibility of disease states or any other biol. state of interest, as well as other applicable non-biol. states of interest. This model first screens genes to reduce noise, applies kmeans correlation-based clustering targeting a large number of clusters, and then uses singular value decompns. (SVD) to extract the single dominant factor (principal component) from each cluster. This generates a statistically significant number of cluster-derived singular factors, that are referred to as metagenes, that characterize multiple

patterns of expression of the genes across samples. The strategy aims to extract multiple such patterns while reducing dimension and smoothing out gene-specific noise through the aggregation within clusters. Formal predictive anal. then uses these metagenes in a Bayesian classification tree anal. This generates multiple recursive partitions of the sample into subgroups (the 'leaves' of the classification tree), and assocs. Bayesian predictive probabilities of outcomes with each subgroup. Overall predictions for an individual sample are then generated by averaging predictions, with appropriate wts., across many such tree models. The model includes the use of iterative out-of-sample, cross-validation predictions leaving each sample out of the data set one at a time, refitting the model from the remaining samples and using it to predict the hold-out case. This rigorously tests the predictive value of a model and mirrors the real-world prognostic context where prediction of new cases as they arise is the major goal.

IT 178967-19-6

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; binary prediction tree modeling with many predictors and its uses in clin. and genomic applications)

L2 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 16 Apr 2004

ACCESSION NUMBER: 2004:311088 CAPLUS

DOCUMENT NUMBER: 140:333564

TITLE: Transgenic mice comprising ASPP1 and ASPP2 gene knockouts and their use in diagnosis and treatment of neurodegenerative diseases

INVENTOR(S): Lu, Xin

PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, Switz.

SOURCE: PCT Int. Appl., 46 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031776	A2	20040415	WO 2003-GB4258	20031003
WO 2004031776	A3	20040527		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: GB 2002-23187 A 20021007

AB The invention relates to a screening method to determine the susceptibility of

a mammal, preferably a human, to abnormal development of the nervous system and including therapeutic methods and compns. for the treatment of

neurodegenerative conditions which result in abnormal expression of a family of polypeptides which induce the apoptotic function of p53. In particular, it relates to transgenic mice comprising ASPP1 and ASPP2 gene knockouts and their use in diagnosis and treatment of neurodegenerative diseases.

IT **679846-54-9**, Protein (mouse gene ASPP2)

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (amino acid sequence; transgenic mice comprising ASPP1 and ASPP2 gene knockouts and their use in diagnosis and treatment of neurodegenerative diseases)

L2 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 16 Apr 2004

ACCESSION NUMBER: 2004:311032 CAPLUS

DOCUMENT NUMBER: 140:332473

TITLE: Protein and cDNA sequences of apoptosis inhibitor protein iASPP and use for treating cancer

INVENTOR(S): Lu, Xin; Kuwabara, Patricia; Selwood, David

PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, Switz.; Genome Research Limited; UCL Cruciform Limited

SOURCE: PCT Int. Appl., 65 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004031229	A2	20040415	WO 2003-GB4296	20031003
WO 2004031229	A3	20040923		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			GB 2002-23193	A 20021007
			GB 2003-6261	A 20030319

AB The invention provides protein and cDNA sequences of apoptosis inhibitor protein iASPP cloned from human and *Caenorhabditis elegans*. The invention relates to a polypeptide, or part thereof, which inhibits the apoptotic activity of the tumor suppressor protein p53 and including screening methods to identify agents which interfere with the activity of said polypeptide.

IT **679518-01-5**

RL: PRP (Properties)

(unclaimed sequence; protein and cDNA sequences of apoptosis inhibitor protein iASPP and use for treating cancer)

L2 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 04 Dec 2003  
 ACCESSION NUMBER: 2003:942767 CAPLUS  
 DOCUMENT NUMBER: 140:40262  
 TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics  
 INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal  
 PATENT ASSIGNEE(S): Duke University, USA  
 SOURCE: PCT Int. Appl., 408 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 3  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
PRIORITY APPLN. INFO.:			US 2002-374547P	P 20020423
			US 2002-420784P	P 20021024
			US 2002-421043P	P 20021025
			US 2002-424680P	P 20021108
			WO 2002-US38221	A 20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].  
 IT 178967-19-6  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)

(amino acid sequence; genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics)

L2 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 24 Nov 2003  
 ACCESSION NUMBER: 2003:917115 CAPLUS  
 DOCUMENT NUMBER: 140:104698  
 TITLE: Rescue of mutants of the tumor suppressor p53 in cancer cells by a designed peptide  
 AUTHOR(S): Issaeva, Natalia; Friedler, Assaf; Bozko, Przemyslaw; Wiman, Klas G.; Fersht, Alan R.; Selivanova, Galina  
 CORPORATE SOURCE: Department of Oncology-Pathology, Cancer Center Karolinska, R8:00, Karolinska Institutet, Karolinska Hospital, Stockholm, SE-171 76, Swed.  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(23), 13303-13307  
 CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB We designed a series of nine-residue peptides that bound to a defined site on the tumor suppressor p53 and stabilized it against denaturation. To test whether the peptides could act as chaperones and rescue the tumor-suppressing function of oncogenic mutants of p53 in living cells, we treated human tumor cells with the fluorescein-labeled peptide Fl-CDB3 (fluorescent derivative of CDB3). Before treatment, the mutant p53 in the cell was predominantly denatured. Fl-CDB3 was taken up into the cytoplasm and nucleus and induced a substantial up-regulation of wild-type p53 protein and representative mutants. The mutants, His-273 and His-175 p53, adopted the active conformation, with a dramatic decrease in the fraction of denatured protein. In all cases, there was p53-dependent induction of expression of the p53 target genes mdm2, gadd45, and p21, accompanied by p53-dependent partial restoration of apoptosis. Fl-CDB3 sensitized cancer cells that carried wild-type p53 to p53-dependent  $\gamma$ -radiation-induced apoptosis. Although Fl-CDB3 did not elicit a full biol. response, it did bind to and rescue p53 in cells and so can serve as a lead for the development of novel drugs for anticancer therapy.

IT 497259-83-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(rescue of mutants of tumor suppressor p53 in cancer cells by a designed peptide)

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 21 Nov 2003

ACCESSION NUMBER: 2003:913280 CAPLUS

DOCUMENT NUMBER: 139:379453

TITLE: Genes showing altered patterns of expression in multiple sclerosis and their diagnostic and therapeutic uses

INVENTOR(S): Dangond, Fernando; Hwang, Daehee

PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA

SOURCE: PCT Int. Appl., 148 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003095618	A2	20031120	WO 2003-US14462	20030507
WO 2003095618	A3	20041021		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004018522	A1	20040129	US 2003-430762	20030506
PRIORITY APPLN. INFO.:			US 2002-379284P	P 20020509
			US 2003-430762	A1 20030506

AB The present invention identifies a number of gene markers whose expression is

altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression. Genes were identified by determination of expression profiling. A large number of genes showing

altered

patterns of expression were identified, with the most discriminatory genes being those for: phosphatidylinositol transfer protein, inducible nitric oxide synthase, CIC-1 (CLCN1) muscle chloride channel protein, placental bikunin (AMBP), receptor kinase ligand LERK-3/Ephrin-A3, GATA-4, thymopoietin, transcription factor E2f-2, S-adenosylmethionine synthetase, carcinoembryonic antigen, the ret oncogene, a G protein-linked receptor (clone GPCR W), GTP- binding protein RALB, tyrosine kinase Syk, LERK-2/Ephrin-B1, ELK1 tyrosine kinase oncogene, transcription factor SL1, phospholipase C, gastricsin (progastricsin), and the D13S824E locus.

IT 178967-19-6

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; genes showing altered patterns of expression in multiple sclerosis and their diagnostic and therapeutic uses)

L2 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 21 Nov 2003

ACCESSION NUMBER: 2003:913187 CAPLUS

DOCUMENT NUMBER: 139:391336

TITLE: Peptides for modulating tumor suppressor protein expression and/or activity

INVENTOR(S): Fersht, Alan; Friedler, Assaf; Wiman, Klas G.; Selivanova, Galina

PATENT ASSIGNEE(S): Medical Research Council, UK

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003095484	A2	20031120	WO 2003-GB2008	20030509
WO 2003095484	A3	20040108		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: GB 2002-10746 A 20020510

AB The invention discloses peptides which alter the expression and/or activity of one or more tumor suppressor proteins. In particular, the invention discloses peptides which increase the expression of p53 and/or the oncogenic mutants of p53 in vivo.

IT 625383-15-5DP, N-terminal fluoresceinated

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(peptides for modulating tumor suppressor protein expression and/or activity)

IT 625383-15-5

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(peptides for modulating tumor suppressor protein expression and/or activity)

L2 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 07 Nov 2003

ACCESSION NUMBER: 2003:875393 CAPLUS

DOCUMENT NUMBER: 139:363045

TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics

INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal

PATENT ASSIGNEE(S): Duke University, USA

SOURCE: PCT Int. Appl., 408 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,				

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,  
 KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,  
 MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
 TR, TT, UA, UG, UZ, VN, YU, ZA, ZW  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,  
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,  
 FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF,  
 CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
 WO 2003091391 A2 20031106 WO 2002-XA38221 20021112  
 W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,  
 DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,  
 KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,  
 MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
 TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
 NE, SN, TD, TG  
 WO 2003091391 A2 20031106 WO 2002-XB38221 20021112  
 W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,  
 DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP,  
 KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN,  
 MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
 TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU,  
 TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,  
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,  
 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
 NE, SN, TD, TG  
 US 2003224383 A1 20031204 US 2002-291885 20021112  
 PRIORITY APPLN. INFO.: US 2002-374547P P 20020423  
 US 2002-420784P P 20021024  
 US 2002-421043P P 20021025  
 US 2002-424680P P 20021108  
 WO 2002-US38221 A 20021112  
 AB Genes whose expression is correlated with an determinant of an  
 atherosclerotic phenotype are provided. Also provided are methods of  
 using the subject atherosclerotic determinant genes in diagnosis and  
 treatment methods, as well as drug screening methods. In addition, reagents  
 and kits thereof that find use in practicing the subject methods are  
 provided. Also provided are methods of determining whether a gene is  
 correlated  
 with a disease phenotype, where correlation is determined using a Bayesian  
 anal.  
 IT 178967-19-6  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
 (Biological study)  
 (amino acid sequence; genes expressed in atherosclerotic tissue and  
 their use in diagnosis and pharmacogenetics)  
 L2 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 29 May 2003  
 ACCESSION NUMBER: 2003:409169 CAPLUS  
 DOCUMENT NUMBER: 138:380506  
 TITLE: Genes that are differentially expressed during

erythropoiesis and their diagnostic and therapeutic uses

INVENTOR(S): Brissette, William H.; Neote, Kuldeep S.; Zagouras, Panayiotis; Zenke, Martin; Lemke, Britt; Hacker, Christine

PATENT ASSIGNEE(S): Pfizer Products Inc., USA; Max-Delbrueck-Centrum Fuer Molekulare Medizin

SOURCE: PCT Int. Appl., 285 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003038130	A2	20030508	WO 2002-XA34888	20021031
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
WO 2003038130	A2	20030508	WO 2002-US34888	20021031
WO 2003038130	A3	20040212		
WO 2003038130	C1	20040422		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2001-335048P P 20011031  
US 2001-335183P P 20011102  
WO 2002-US34888 A 20021031

AB The present invention provides mol. targets that regulate erythropoiesis. Groups of genes or their encoded gene products comprise panels of the invention and may be used in therapeutic intervention, therapeutic agent screening, and in diagnostic methods for diseases and/or disorders of erythropoiesis. The panels were discovered using gene expression profiling of erythroid progenitors with Affymetrix HU6800 and HG-U95Av2 chips. Cells from an in vitro growth and differentiation system of SCF-Epo dependent human erythroid progenitors, E-cadherin+/CD36+ progenitors, cord blood, or CD34+ peripheral blood stem cells were analyzed. The HU6800 chip contains probes from 13,000 genes with a potential role in cell growth, proliferation, and differentiation and the HG-U95Av2 chip contains 12,000 full-length, functionally-characterized

genes. [This abstract record is one of two records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT 178967-19-6

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(amino acid sequence; genes that are differentially expressed during erythropoiesis and their diagnostic and therapeutic uses)

L2 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 18 Apr 2003

ACCESSION NUMBER: 2003:301181 CAPLUS

DOCUMENT NUMBER: 138:316493

TITLE: Novel human proteins and cDNAs and their use in drug screening and disease diagnosis and treatment

INVENTOR(S): Alsobrook, John P., II; Burgess, Catherine E.; Catterton, Elina; Chant, John S.; Chaudhuri, Amitabha; Edinger, Shlomit R.; Gerlach, Valerie L.; Giot, Loic; Gorman, Linda; Guo, Xiaojia; Kekuda, Ramesh; Mezes, Peter S.; Millet, Isabelle; Ooi, Chean Eng; Patturajan, Meera; Rieger, Daniel K.; Spytek, Kimberly A.; Taupier, Raymond J., Jr.; Zerhusen, Bryan D.; Zhong, Haihong; Zhong, Mei

PATENT ASSIGNEE(S): Curagen Corporation, USA

SOURCE: PCT Int. Appl., 253 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 148

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003031571	A2	20030417	WO 2002-US31357	20021002
WO 2003031571	A3	20030731		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG				
US 2004014058	A1	20040122	US 2002-262445	20021001
US 2004038877	A1	20040226	US 2002-262839	20021001
PRIORITY APPLN. INFO.:			US 2001-327454P	P 20011005
			US 2001-327917P	P 20011009
			US 2001-328029P	P 20011009
			US 2001-328056P	P 20011009
			US 2001-328849P	P 20011012
			US 2001-329414P	P 20011015
			US 2001-330142P	P 20011017
			US 2001-341058P	P 20011022

US 2001-343629P	P 20011024
US 2001-349575P	P 20011029
US 2001-346357P	P 20011101
US 2002-391342P	P 20020625
US 2002-262445	A2 20021001
US 2001-326483P	P 20011002
US 2001-327342P	P 20011005
US 2001-328044P	P 20011009
US 2001-339266P	P 20011024
US 2002-371972P	P 20020412
US 2002-371980P	P 20020412
US 2002-373261P	P 20020417
US 2002-373805P	P 20020419
US 2002-374738P	P 20020423
US 2002-381101P	P 20020516
US 2002-381635P	P 20020517
US 2002-383830P	P 20020529

AB Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies that immunospecifically bind to the polypeptide, as well as derivs., variants, mutants, or fragments of the novel polypeptide, polynucleotide, or antibody specific to the polypeptide. Vectors, host cells, antibodies and recombinant methods for producing the polypeptides and polynucleotides, as well as methods for using same are also included. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins. Thus, 33 novel human cDNAs and the encoded proteins are disclosed. These display sequence homol. to various proteins, e.g., hepatocellular carcinoma-associated antigen, ferritin light chain, tumor suppressor p53-binding protein 2, etc. The expression of the genes for these proteins in various normal and diseased tissues were examined SNPs in these nucleic acids were identified. Proteins binding to TRAF and to DAPK3 were also identified.

IT 514228-34-3, Protein NOV20a (human) 514228-35-4, Protein NOV20b (human) 514228-36-5, Protein NOV20c (human)  
 RL: ANT (Analyte); ARG (Analytical reagent use); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)  
 (amino acid sequence; novel human proteins and cDNAs and their use in drug screening and disease diagnosis and treatment)

L2 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 21 Feb 2003

ACCESSION NUMBER: 2003:133296 CAPLUS

DOCUMENT NUMBER: 138:166255

TITLE: Stabilization of the native conformation of a mutant tumor suppressor protein p53 and other mutant proteins using CDB3 peptide and other biomolecules and application to treatment of cancer and other diseases

INVENTOR(S): Friedler, Assaf; Fersht, Alan

PATENT ASSIGNEE(S): Medical Research Council, UK

SOURCE: PCT Int. Appl., 73 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003014144	A2	20030220	WO 2002-GB3668	20020809
WO 2003014144	A3	20031127		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1414846	A2	20040506	EP 2002-749128	20020809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2005008653	A1	20050113	US 2004-775679	20040210
PRIORITY APPLN. INFO.:			GB 2001-19557	A 20010810
			GB 2001-27917	A 20011121
			GB 2002-10740	A 20020510
			WO 2002-GB3668	W 20020809

AB We disclose a method of stabilizing the native state of a polypeptide, the method comprising exposing the polypeptide to a stabilizing mol. capable of binding to the polypeptide at a site which at least partially overlaps a functional site in its native state. The authors describe the isolation and identification of a stabilizing peptide CDB3, which is capable of binding the tumor suppressor protein p53 near its DNA binding site, and stabilizing the native form of the protein. Since the binding of DNA itself stabilizes p53 core domain, and it binds very tightly, stabilization by a peptide such as CDB3 is needed only for mutants where DNA binding is impaired because mutant p53 is in denatured conformation. Once the protein has bound DNA, the peptide is not needed any more. The ability of CDB3 to induce refolding of p53 core domain, together with the observation that DNA can displace it from p53, led the authors to propose the a "chaperone" mechanism for rescuing a denatured oncogenic protein: CDB3 binds only the native state of the oncogenic protein which is able to bind DNA, probably immediately on biosynthesis, and therefore shifts the equilibrium towards the native state. Then DNA can bind the protein, displacing the peptide, which is free again to bind another protein mol. Exemplary design of potential P53 core domain binding peptides, screening of the CDB peptides for binding p53 core domain, identification of the P53 core domain binding peptide CDB3, characterization of CDB3-P53 core domain binding and binding of fluorescein-labeled CDB3 are reported. Stabilizing mols. and/or compns. of the invention can be used in the treatment of any animal or human disease where errors in protein conformation, folding and aggregation contribute to the disease. Examples include cancer, cystic fibrosis and neuro-degeneration. In a particularly preferred embodiment, the disease is cancer.

IT 497259-83-3P

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(CDB3; stabilization of native conformation of human mutant tumor suppressor protein p53 and other mutant proteins using CDB3 peptide and other biomols. and application to treatment of cancer and other diseases)

IT 497259-83-3DP, fluorescein labeled

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(stabilization of native conformation of human mutant tumor suppressor protein p53 and other mutant proteins using CDB3 peptide and other biomols. and application to treatment of cancer and other diseases)

L2 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 07 Feb 2003

ACCESSION NUMBER: 2003:97550 CAPLUS

DOCUMENT NUMBER: 138:164674

TITLE: Molecular markers for hepatocellular carcinoma and their use in diagnosis and therapy

INVENTOR(S): Debuschewitz, Sabine; Jobst, Juergen; Kaiser, Stephan

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 98 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010336	A2	20030206	WO 2002-EP8305	20020725
WO 2003010336	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10136273	A1	20030213	DE 2001-10136273	20010725
EP 1507871	A2	20050223	EP 2002-790191	20020725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
WO 2004011945	A2	20040205	WO 2003-EP8243	20030725
WO 2004011945	A3	20040603		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,				

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,  
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG  
PRIORITY APPLN. INFO.: DE 2001-10136273 A 20010725  
WO 2002-EP8305 W 20020725

AB The invention relates to mol. markers occurring for hepatocellular carcinoma. The invention more particularly comprises gene sequences or peptides coded thereby which can be regulated upwards or downwards for hepatic cell carcinoma (HCC) in relation to healthy, normal liver cells in the expression thereof. The invention also relates to the use of said sequences in the diagnosis and/or therapy of HCC and for screening purposes in order to identify novel active ingredients for HCC. The invention also relates to an HCC specific cluster as a unique diagnostic agent for HCC.

IT 178967-19-6

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(amino acid sequence; mol. markers for hepatocellular carcinoma)

L2 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED      Entered STN: 29 Dec 2002

ACCESSION NUMBER: 2002:978557 CAPLUS

DOCUMENT NUMBER: 138:49915

**TITLE:** Novel p53BP2 compounds for therapy and diagnosis and methods for using same

INVENTOR(S): Nicolette, Charles A.

PATENT ASSIGNEE(S):

SOURCE: U.S. Pat. Appl. Publ., 39 pp.

CODEN: USXXCO

DOCUMENT TYPE:

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

**PATENT INFORMATION:**

PATENT NO.

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002197243	A1	20021226	US 2002-114091	20020401
WO 2003075831	A2	20030918	WO 2002-US10133	20020401
WO 2003075831	A3	20040617		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2001-280794P P 20010330

AB The present invention provides methods and compns. for detecting, diagnosing, prognosis and monitoring the progress of p53BP2-related cancers and malignancies and kits for use in said methods. Further provided are methods for screening to identify agonists and antagonists of cancer antigens associated with p53BP2-related cancers and malignancies. A composition comprising a polynucleotide encoding at least one immunogenic ligand and a host cell comprising the polynucleotide are claimed. The

composition further comprises a pharmaceutically acceptable carrier. The host cell is a dendritic cell.

IT **479014-21-6P**

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)  
(amino acid sequence, immunogenic compound; novel p53BP2 compds. for cancer therapy and diagnosis and methods for using same)

L2 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 11 Oct 2002

ACCESSION NUMBER: 2002:777632 CAPLUS

DOCUMENT NUMBER: 137:293524

TITLE: Chimeric protein comprising immunoglobulin consensus framework and CDR sequence from p53-binding protein p53BP2 for eliciting an anti-tumor response

INVENTOR(S): Nicolette, Charles A.; Soltis, Daniel A.

PATENT ASSIGNEE(S): Purdue Pharma L.P., USA

SOURCE: PCT Int. Appl., 100 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002078609	A2	20021010	WO 2002-US10224	20020401
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2001-280733P	P 20010330

AB The present invention provides IgS specific for p53BP2 ligand polypeptides. In a preferred embodiment, the present invention provides a variant of an Ig variable domain, wherein the Ig variable domain contains (A) at least one CDR region and (B) framework regions flanking the CDR, and the variant includes: (a) the CDR region having added or substituted therein at least one binding sequence, and (b) the flanking framework regions, wherein the binding sequence is heterologous to the CDR and the binding sequence is derived from a human ligand having immunogenic properties relevant to human lung cancer. In a preferred embodiment, the binding sequence is an antigenic sequence. In a further preferred embodiment, the variant contains a variable domain lacking an intrachain disulfide bond.

IT **469356-94-3**

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; chimeric protein comprising Ig CDRs and human lung tumor antigen p53BP2 for eliciting an anti-tumor response)

L2 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 16 Nov 2001  
 ACCESSION NUMBER: 2001:832384 CAPLUS  
 DOCUMENT NUMBER: 136:116397  
 TITLE: ASPP proteins specifically stimulate the apoptotic function of p53  
 AUTHOR(S): Samuels-Lev, Yarden; O'Connor, Daniel J.; Bergamaschi, Daniele; Trigiante, Giuseppe; Hsieh, Jung-Kuang; Zhong, Shan; Campargue, Isabelle; Naumovski, Louie; Crook, Tim; Lu, Xin  
 CORPORATE SOURCE: Ludwig Institute for Cancer Research, Imperial College School of Medicine, London, W2 1PG, UK  
 SOURCE: Molecular Cell (2001), 8(4), 781-794  
 CODEN: MOCEFL; ISSN: 1097-2765  
 PUBLISHER: Cell Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The authors identified a family of proteins termed ASPP. ASPP1 is a protein homologous to 53BP2, the C-terminal half of ASPP2. ASPP proteins interact with p53 and specifically enhance p53-induced apoptosis but not cell cycle arrest. Inhibition of endogenous ASPP function suppresses the apoptotic function of endogenous p53 in response to apoptotic stimuli. ASPP enhance the DNA binding and transactivation function of p53 on the promoters of proapoptotic genes in vivo. Two tumor-derived p53 mutants with reduced apoptotic function were defective in cooperating with ASPP in apoptosis induction. The expression of ASPP is frequently down-regulated in human breast carcinomas expressing wild-type p53 but not mutant p53. Therefore, ASPP regulate the tumor suppression function of p53 in vivo.  
 IT 389661-99-8  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (amino acid sequence; cDNA sequences of ASPP proteins that specifically stimulate apoptotic function of p53 and fail to cooperate with tumor-derived p53 mutants)  
 REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 24 Aug 2001  
 ACCESSION NUMBER: 2001:618209 CAPLUS  
 DOCUMENT NUMBER: 135:193985  
 TITLE: Genes expressed in tumor cells and their use as diagnostic markers and the assessment of tumors to chemotherapy  
 INVENTOR(S): Roth, Frederick P.; Van Huffel, Christophe; White, James V.; Shyjan, Andrew W.  
 PATENT ASSIGNEE(S): Millennium Predictive Medicine, Inc., USA  
 SOURCE: PCT Int. Appl., 122 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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Searcher : Shears 571-272-2528

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WO 2001061050	A2	20010823	WO 2001-US5301	20010216
WO 2001061050	A3	20030227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002120004	A1	20020829	US 2001-788099	20010216
US 2003129629	A1	20030710	US 2002-272111	20021016
PRIORITY APPLN. INFO.:			US 2000-183265P	P 20000217
			US 2001-788099	A1 20010216

AB The present invention is directed to the identification of markers that can be used to determine the sensitivity of cancer cells to a therapeutic agent. The present invention is also directed to the identification of therapeutic targets. Nucleic acid arrays were used to determine the level of expression of sequences (genes) found in 60 different solid tumor cancer cell lines selected from the NCI 60 cancer cell line series. Expression anal. was used to identify markers associated with sensitivity to certain chemotherapeutic agents.

IT **355485-67-5**

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(amino acid sequence; genes expressed in tumor cells and their use as diagnostic markers and assessment of tumors to chemotherapy)

L2 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 24 Aug 2001

ACCESSION NUMBER: 2001:618207 CAPLUS

DOCUMENT NUMBER: 135:190398

TITLE: Nucleic acid markers useful for the identification, assessment, prevention and therapy of human cancers

INVENTOR(S): Roth, Frederick P.; Van Huffel, Christophe; White, James V.; Shyjan, Andrew W.

PATENT ASSIGNEE(S): Millennium Predictive Medicine, Inc., USA

SOURCE: PCT Int. Appl., 126 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2001061048	A2	20010823	WO 2001-US5263	20010216
WO 2001061048	A3	20030123		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,				

ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002051978 A1 20020502 US 2001-788100 20010216

PRIORITY APPLN. INFO.: US 2000-183312P P 20000217

AB The present invention is directed to the identification of markers that can be used to determine the sensitivity of cancer cells to a therapeutic agent. The present invention is also directed to the identification of therapeutic targets. Nucleic acid arrays were used to determine the level of

expression of sequences (genes) found in 60 different solid tumor cancer cell lines selected from the NCI 60 cancer cell line series. Expression anal. was used to identify markers associated with sensitivity to certain chemotherapeutic agents.

IT 355485-67-5

RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses) (amino acid sequence; nucleic acid markers useful for the identification, assessment, prevention and therapy of human cancers)

L2 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 02 Jul 1996

ACCESSION NUMBER: 1996:381500 CAPLUS

DOCUMENT NUMBER: 125:106785

TITLE: The p53-binding protein 53BP2 also interacts with Bcl2 and impedes cell cycle progression at G2/M

AUTHOR(S): Naumovski, Louie; Cleary, Michael L.

CORPORATE SOURCE: Dep. Pediatrics, Div. Hematology/Oncology, Stanford, CA, 94305, USA

SOURCE: Molecular and Cellular Biology (1996), 16(7), 3884-3892

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Using the yeast two-hybrid system, we have isolated a cDNA (designated BBP, for Bcl2-binding protein) for a protein (Bbp) that interacts with Bcl2. Bbp is identical to 53BP2, a partial clone of which was previously isolated in a two-hybrid screen for proteins that interact with p53. In this study, we show that specific interactions of Bbp/53BP2 with either Bcl2 or p53 require its ankyrin repeats and SH3 domain. These interactions can be reproduced in vitro with bacterially expressed fusion proteins, and competition expts. indicate that Bcl2 prevents p53 from binding to Bbp/53BP2. BBP/53BP2 mRNA is abundant in most cell lines examined, but the protein cannot be stably expressed in a variety of cell types by transfection. In transiently transfected cells, Bbp partially colocalizes with Bcl2 in the cytoplasm and results in an increased number of cells at G2/M, possibly accounting for the inability to obtain stable transfectants expressing the protein. These results demonstrate that a single protein can interact with either Bcl2 or p53 both in yeast cells and in vitro. The in vivo significance of these interactions and their potential consequences for cell cycle progression and cell death remain to be determined

IT 178967-19-6, Protein (human Bcl2 p53 binding reduced)

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
 (amino acid sequence; p53-binding protein 53BP2 also interacts with Bcl2 and impedes cell cycle progression at G2/M)

E1 THROUGH E15 ASSIGNED

FILE 'REGISTRY' ENTERED AT 15:04:12 ON 03 MAR 2005

L3 15 SEA FILE=REGISTRY ABB=ON PLU=ON (178967-19-6/BI OR 497259-83-3/BI OR 355485-67-5/BI OR 625383-15-5/BI OR 389661-99-8/BI OR 469356-94-3/BI OR 479014-21-6/BI OR 514228-34-3/BI OR 514228-35-4/BI OR 514228-36-5/BI OR 606804-01-7/BI OR 679518-01-5/BI OR 679846-54-9/BI OR 753036-25-8/BI OR 795109-26-1/BI)

L4 15 L1 AND L3

L4 ANSWER 1 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN

RN 795109-26-1 REGISTRY

CN Protein (human tumor suppressor gene ASPP2 (apoptosis stimulating proteins of p53 2)) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 4: PN: US20040228866 SEQID: 4 claimed protein

CI MAN

SQL 1128

SEQ 1 MMPMFLTVYL SNNEQHFTEV PVTPETICRD VVDLCKEPGE SDCHLAEVWC  
 51 GSERPVADNE RMFDVLQRFG SQRNEVRFFL RHERPPGRDI VSGPRSQDPS  
 101 LKRNGVKVPG EYRRKENGVN SPRMDLTLAE LQEMASRQQQ QIEAQQQQLLA  
 151 TKEQRLKFLK QDQDQQQQV AEQEKLKRLK EIAENQEAKL KKVRALKGHV  
 201 EQKRLSNGKL VEEIEQMNNL FQQKQRELVL AVSKVEELTR QLEMLKNGRI  
 251 DSHHDNQSAV AELDRLYKEL QLRNKLNQEQQ NAKLQQQREC LNKRNSEVAV  
 301 MDKRVNELRD RLWKKKAALQ QKENLPVSSD GNLPQQAASA PSRVAAVGPY  
 351 IQSSTMPMPR MP RPELLVKA PA LPDGSLSVIA SEGPMMKIQTL PNMRSGAASQ  
 401 TKGSKIH PVG PDWSPSNADL FPSQGSASVP QSTGNALDQV DDGEVPLREK  
 451 EKKVRPFSMF DAVDQSNAPP SFGTLRKNQS SEDILRDAQV ANKNAVKVPP  
 501 PVPTKPKQIN LPYFGQTNQP PSDIKPDGSS QQLSTVVPSM GTKPKPAGQQ  
 551 PRVLLSPSIP SVGQDQTLSP GSKQESPPAA AVRFTPQPS KDTLLPPFRK  
 601 PQTVAASSIY SMYTQQQAPG KNFQQAVQSA LTKTHTRGPH FSSVYGPVVI  
 651 AAAQNQQQHP ENIYSNSQGK PGSPEPETEP VSSVQENHEN ERIPRPLSPT  
 701 KLLPFLSNPY RNQSDADLEA LRKKLSSNAPR PLKKRSSITE PEGPNPGPNIQ  
 751 KLLYQRTTIA AMETISVPSY PSKSASVTAS SESPVEIQNP YLHVEPEKEV  
 801 VSLVPESLSP EDVGNASTEN SDMPAPSPGL DYEPEGVPDN SPNLQNNPEE  
 851 PNPEAPHVLD VYLEEYPPYP PPPYPSGEPE GPGEDSVSMR PPEITGQVSL  
 901 PPGKRTNLRK TGSERIAHGM RVKFNPLALL LDSSLEGEFD LVQRIIYEV  
 951 DPSLPNDEGI TALHNACVAG HTEIVKFLVQ FGVNVAADS DGWTPLHCAA  
 1001 SCNNVQVCKF LVEGAAVFA MTYSDMOTAA DKCEEMEEGY TOCSQFLYGV  
 1051 QEKGIMNKG VIYALWDYEP QNDDELPMKE GDCMTIIHRE DEDEIEWWWA

== =====

1101 RLNDKEGYVP RNLLGLYPRI KPRQRSLA  
 HITS AT: 1089-1097

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 141:421046

L4 ANSWER 2 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN

RN 753036-25-8 REGISTRY  
 CN Tumor-associated protein (human clone WO2004076614-SEQID-178 fragment)  
 (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 297: PN: WO2004076614 SEQID: 178 claimed protein  
 CI MAN  
 SQL 1101

SEQ 1 SACLGLPKCW ITGVSHHDQP LVFKKERPVA DNERMFVLO RFGSQRNEVR  
 51 FFLRHERPPG RDIVSGPRSQ DPSLKRNGVK VPGEYRRKEN GVNSPRMDLT  
 101 LAELQEMASR QQQIEAQQQ LLATKEQRLK FLKQDQRRQQ QVVAEQEKLK  
 151 RLKEIAENQE AKLKKVRAK GHVEQKRLSN GKLVEEIEQM NNLFQQKQRE  
 201 LVLAVSKVEE LTRQLEMLKN GRIDSHHDNQ SAVAELDRLY KELQLRNKLN  
 251 QEONAKLQQQ RECLNKRNSV VAVMDKRVNE LRDRILWKKKA ALQQKENLPV  
 301 SSDGNLPQQA ASAPSRAAV GPYIQSSTMP RMPSRPELLV KPALPDGSLV  
 351 IQASEGPMKI QTLPNMRSGA ASQTKGSKIH PVGPDWSPSN ADLFPQSQGSA  
 401 SVPQSTGNAL DQVDDGEVPL REKEKKVRF P SMFDAVDQSN APPSFGTLRK  
 451 NQSSEDLRD AQVANKNVAK VPPPVPDKPK QINLPYFGQT NQPPSDIKPD  
 501 GSSQQLSTVV PSMGTPKPKA GQOPRVLSP SIPSVGQDQT LSPGSKQESP  
 551 PAAAVRPFTP QPSKDTLLPP FRKPQTVAAAS SIYSMYTQQQ APGKNFQQAV  
 601 QSALTKTHTR GPHFSSVYKG PVIAAAQNQQ QHPENIYSNS QGKPGSPEPE  
 651 TEPVSSVQEN HENERIPRPL SPTKLLPFLS NPYRNQSDAD LEALRKKLSN  
 701 APRPLKKRSS ITEPEGPNGP NIQKLLYQRT TIAAMETISV PSYPSKSASV  
 751 TASSESPVEI QNPYLYHVEPE KEVVSILVPE LSPEDVGNAS TENSMDPAPS  
 801 PGLDYEPGV PDNSPNLQNN PEEPNPEAPH VLDVYLEEYP PYPPPPYPSG  
 851 EPEGPGEDSV SMRPPETGQ VSLPPGKRTN LRKTGSERIA HGMRVKFNPL  
 901 ALLLDSSLEG EFDLVQRIY EVDDPSLPND EGITALHNAD CAGHTEIVKF  
 951 LVQFGVNVNA ADSDGWTPLH CAASCNNVQV CKFLVESGAA VFAMTYSDMQ  
 1001 TAADKCEEME EGYTQCSQFL YGVQEKGIM NKGVIYALWD YEPQNDDELP  
 1051 MKEGDCMTII HREDEDEIEW WWARLNDKEG YVPRNLLGLY PRIKPRQRSL

=====

1101 A  
 HITS AT: 1062-1070

REFERENCE 1: 141:258758

L4 ANSWER 3 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 679846-54-9 REGISTRY  
 CN Protein (mouse gene ASPP2) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 11: PN: WO2004031776 FIGURE: 4 claimed sequence  
 CI MAN  
 SQL 1128

SEQ 1 MMPMFITVYL SNNEQHFTEV PVTPETICRD VVDLCKEPGE SDCHLAEVWC  
 51 GSERPVADNE RMFDVLQRFQ SQRNEVRFFL RHERPPGRDI VSGPRSQDPS  
 101 LKRNGVKVPG EYRRKENGVN SPRMDLTLAE LQEMASRQQQ QIEAQQQLLA  
 151 TKEQLRKFLK QODQRQQQQV AEQEKLKRLK EIAENQEAKL KKVRALKGHV  
 201 EQKRLSNGKL VEEIEQMNNL FQOKQRELVL AVSKVEELTR QLEMLKNGRI  
 251 DSHHDNQSAV AEELDRLYKEL QLRNKLNQEQ NAKLQQQREC LNKRNSEAV  
 301 MDKRVNELRD RLWKKKAALQ QKENLPVSSD GNLPQQAASA PSRVAAVGPY  
 351 IQSSTMPRMP SRPELLVKA LPDGLSVIQA SEGPMKIQTL PNMRSGAASQ  
 401 TKGSKIHPVG PDWSPSNADL FPSQGSASVP QSTGNALDQV DDGEVPLREK  
 451 EKKVRPFSMF DAVDQSNAPP SFGTLLRKNQS SEDILRDAQV ANKNAVKVPP  
 501 PVPTKPKQIN LPYFGQTNQP PSDIKPDGSS QQLSTVVPSM GTKPKPAGQQ  
 551 PRVLLSPSIP SVGQDQTLSP GSKQESPPAA AVRPFPTPQPS KDTLLPPFRK

601 PQTVAASSIY SMYTQQQAPG KNFQQAVQSA LTKTHTRGPH FSSVYGKPVI  
 651 AAAQNQQQHP ENIYSNSQGK PGSPEPETEP VSSVQENHEN ERIPRPLSPT  
 701 KLLPFLSNPY RNQSDADLEA LRKKLSSNAPR PLKKRSSITE PEGPNQPNQ  
 751 KLLYQRTTIA AMETISVPSY PSKSASVTAS SESPVEIQNP YLHVEPEKEV  
 801 VSLVPESLSP EDVGNASTEN SDMPAPSPGL DYEPGVPDN SPNLQNNPEE  
 851 PNPEAPHVLD VYLEEYPPYP PPPYPSGEPE GPGEDSVSMR PPEITGQVSL  
 901 PPGKRTNLRK TGSERIAHGM RVKFNPLALL LDSSLEGEFD LVQRIIYEV  
 951 DPSLPNDEGI TALHNACAG HTEIVKFLVQ FGVNVAADS DGWTPLHCAA  
 1001 SCNNVQVCKF LVEGAAVFA MTYSDMQTAA DKCEEMEEGY TQCSQFLYGV  
 1051 QEKGIMNKG VIYALWDYEP QNDDELPMK EGDCMTIIHR DEDEIEWWA  
 == =====

1101 RLNDKEGYVP RNLLGLYPRI KPRQRSLA  
 HITS AT: 1089-1097

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 140:333564

L4 ANSWER 4 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 679518-01-5 REGISTRY  
 CN 7: PN: WO2004031229 FIGURE: 10 unclaimed sequence (9CI) (CA INDEX NAME)  
 CI MAN  
 SQL 179

SEQ 1 DDPSPNDEG ITALHNAVCA GHTEIVKFLV QFGVNVAAD SDGWTPLHCA  
 51 ASCNNVQVCK LVEGAAVF AMTYSDMQTA ADKCEEMEEG YTQCSQFLYGV  
 101 VQEKGIMNKG VIYALWDYEP QNDDELPMK EGDCMTIIHR EDEDEIEWW  
 == =====

151 ARLNDKEGYV PRNLLGLYPR IKPRQRSLA  
 HITS AT: 140-148

REFERENCE 1: 140:332473

L4 ANSWER 5 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 625383-15-5 REGISTRY  
 CN L-Tryptophanamide, L-arginyl-L- $\alpha$ -glutamyl-L- $\alpha$ -aspartyl-L- $\alpha$ -glutamyl-L- $\alpha$ -aspartyl-L- $\alpha$ -glutamyl-L-isoleucyl-L- $\alpha$ -glutamyl- (9CI) (CA INDEX NAME)  
 SQL 9

SEQ 1 REDEDEIEW  
 =====

HITS AT: 1-9

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 139:391336

L4 ANSWER 6 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 606804-01-7 REGISTRY  
 CN TP53BP2 protein (human clone MGC:65089 IMAGE:4537206) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN GenBank AAH58918  
 CN GenBank AAH58918 (Translated from: GenBank BC058918)  
 CI MAN

SQL 1127

SEQ 1 MPMFLTVYLS NNEQHFTEV P VTPETICRDV VDLCKEPGES DCHLAEVWCG  
 51 SERPVADNER MFDVLQRFGS QRNEVRFPLR HERPPGRDIV SGPRSQDPSL  
 101 KRNGVKVPGE YRRKENGVNS PRMDLTLAEL QEMASRQQQQ IEAQQQLLAT  
 151 KEQLKFLKQ QDQRQQQQVA EOEKLIKRLKE IAENQEAKLK KVRAKGHVE  
 201 QKRLSNGKLV EEIEQMNLF QQKQRELVLA VSKVEELTRQ LEMLKNGRID  
 251 SHHDNQSAVA ELDRLYKELQ LRNKLNQEQN AKLQQQRECL NKRNEVAVM  
 301 DKRVNELRDR LWKKKAALQQ KENLPVSSDG NLPQQAASAP SRVAAVGPYI  
 351 QSSTMPRMPMS RPELLVKPAL PDGSLVIQAS EGPMKIQTLP NMRSGAASQT  
 401 KGSKIHPVGP DWSPSNADLF PSQGSASVPO STGNALDQVD DGEVPLREKE  
 451 KKVRPFSMFD AVDQSNAPPS FGTLRKNQSS EDILRDAQVA NKNVAKVPPP  
 501 VPTKPKQINL PYFGQTNQPP SDIKPDGSSQ QLSTVVPSMG TKPKPAGQQP  
 551 RVLLSPSIPS VGQDQTLSPG SKQESPPAAA VRPFTPQPSK DTLLPPFRKP  
 601 QTVAASSIYS MYTQQQAPGK NFQQAVQSL TKTHTRGPHF SSVYGPVIA  
 651 AAQNQQQHPE NIYSNSQGKP GSPEPETEPV SSVQENHENE RIPRPLSPTK  
 701 LLPFLSNPYR NQSDADLEAL RKKLSNAPRP LKKRSSITEP EGPNGPNIQK  
 751 LLYQRTTIAA METISVPSYP SKSASVTASS ESPVEIQNPY LHVEPEKEVV  
 801 SLVPESLSPE DVGNASTENS DMPAPSPGLD YEPEGVPDNS PNLLQNNPEEP  
 851 NPEAPHVLDV YLEEYPPYPP PPYPSGEPEG PGEDSVSMRP PEITGQVSLP  
 901 PGKRTNLRKT GSERIAHGMR VKFNPALLL DSSLEGEFDL VQRIIYEVDD  
 951 PSLPNDEGIT ALHNAVCAGH TEIVKFLVQF GVNVAADSD GWTPLHCAAS  
 1001 CNNVQVCKFL VESGAAVFAM TYSDMQTAAD KCEEMEEGYT QCSQFLYGVQ  
 1051 EKMGIMNKGV IYALWDYEPO NDDELPMEKG DCMTIHHRED EDEIEWWWAR

====

1101 LNDKEGYVPR NLLGLYPRIK PRQRSIA  
 HITS AT: 1088-1096

REFERENCE 1: 142:18208

L4 ANSWER 7 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN

RN 514228-36-5 REGISTRY

CN Protein NOV20c (human) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 65: PN: WO03031571 SEQID: 66 claimed protein

CI MAN

SQL 1001

SEQ 1 MFDVLQRFGS QRNEVRFPLR HERPPGRDIV SGPRSQDPSL KRNGVKVPGE  
 51 YRRKENGVNS PRMDLTLAEL QEMASRQQQQ IEAQQQLLAT KEQLKFLKQ  
 101 QDQRQQQQVA EOEKLIKRLKE IAENQEAKLK KVRAKGHVE QKRLSNGKLV  
 151 EEIEQMNLF QQKQRELVLA VSKVEELTRQ LEMLKNGRID SHHDNQSAVA  
 201 ELDRLYKELQ LRNKLNQEQN AKLQQQRECL NKRNEVAVM DKRVNELRDR  
 251 LWKKKAALQQ KENLPVSSDG NLPQQAASAP SRVAAVGPYI QSSTMPRMPMS  
 301 RPELLVKPAL PDGSLVIQAS EGPMKIQTLP NMRSGAASQT KGSKIHPVGP  
 351 DWSPSNADLF PSQGSASVPO STGNALDQVD DGEVPLREKE KKVRPFSMFD  
 401 AVDQSNAPPS FGTLRKNQSS EDILRDAQVA NKNVAKVPPP VPTKPKQINL  
 451 PYFGQTNQPP SDIKPDGSSQ QLSTVVPSMG TKPKPAGQQP RVLLSPSIPS  
 501 VGQDQTLSPG SKQESPPAAA VRPFTPQPSK DTLLPPFRKP QTVAASSIYS  
 551 MYTQQQAPGK NFQQAVQSL TKTHTRGPHF SSVYGPVIA AAQNQQQHPE  
 601 NIYSNSQGKP GSPEPETEPV SSVQENHENE RIPRPLSPTK LLPFLSNPYR  
 651 NQSDADLEAL RKKLSNAPRP LKKRSSITEP EGPNGPNIQK LLYQRTTIAA  
 701 METISVPSYP SKSASVTASS ESPVEIQNPY VLDVYLEEY PYPYPPYPSG  
 751 EPEGPGEDSV SMRPEITGQ VSLPPGKRTN LRKTGSERIA HGMRVKFNPL  
 801 ALLLDSSLEG EFDLVQRIIY EVDDPSLPND EGITALHNAV CAGHTEIVKF  
 851 LVQFGNVNA ADSDGWTPLH CAASCNNVQV CKFLVESGAA VFAMTYSDMQ

901 TAADKCEEME EGYTQCSQFL YGVQEKGIM NKGVIYALWD YEPQNDDELP  
 951 MKEGDCMTII HREDEDEIEW WWARLNDKEG YVPRNLLGLY PRIKPRQRSL  
 =====

1001 A  
 HITS AT: 962-970

REFERENCE 1: 138:316493

L4 ANSWER 8 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 514228-35-4 REGISTRY  
 CN Protein NOV20b (human) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 63: PN: WO03031571 SEQID: 64 claimed protein  
 CI MAN  
 SQL 1068

SEQ 1 MRFGSKMMMP FLTIVYLSNNE QHFTEVPVTP ETICRDVVLD CKEPGESDCH  
 51 LAEVWCGSER PVADNERMFD VLQRFGSQRN EVRFFLRHER PPGRDIVSGP  
 101 RSQDPSLKR GVKVPGEYRR KENGVNSPRM DLT LAELQEM ASRQQQQIEA  
 151 QQQLLATKEQ RLKFLKQDQ RQQQQVAEAE KLKRLKEIAE NQEAKLKKVR  
 201 ALKGHVEQKR LSNGKLVEEI EQMNNLFQOK QRELVLAVSK VEELTRQLEM  
 251 LKNGRIDSHH DNQSAVAEEL RLYKELQLRN KLNQEQNAKL QQRECLNKR  
 301 NSEVAVMDKR VNELRDRRLWK KKAALQQKEN LPVSSDGNLP QQAASAPSRR  
 351 AAVGPYIQSS TMPRMPSRPE LLVKPALPDG SLVIQASEGP MKIQTLPNMR  
 401 SGAASQTKGS KIHPVGPDWS PSNADLFPQG GSASVPQSTG NALDQVDDGE  
 451 VPLREKEKKV RPFMSMFDADV QSNAPPSFGT LRKNQSSEDI LRDAQVANKN  
 501 VAKVPPPVT KPKQINLPYF GQTNQPPSDI KPDGSSQQLS TVVPSMGTKP  
 551 KPAGQQRVRL LSPSIPSVGQ DQTLSPGSKQ ESPPAAAVRP FTPQPSKDTL  
 601 LPPFRKPQTV AASSIYSMYT QQQAPGKNFQ QAVQSLTKT HTRGPHFSSV  
 651 YGKPVIAAAQ NQQQHPEXIY SNSQGKPGSP EPETEPVSSV QENHENERIP  
 701 RPLSPTKLLP FLSNPYRNQS DADLEALRKK LSNAPRPLKK RSSITEPEGP  
 751 NGPNIQKLLY QRTTIAAMET ISVPSPSKS ASVTASSESP VEIQNPHVLD  
 801 VYLEYPPYP PPPYPSGEPE GPGEDSVSMR PPEITGQVSL PPGKRTNLRK  
 851 TGSERIAHGM RVKFNPLALL LDSSLEGEFD LVQRIIYEV DPSLPNDEGI  
 901 TALHNACAG HTEIVKFLVQ FGVNVNAADS DGWTPLHCAA SCNNVQVCKF  
 951 LVESGAAVFA MTYSDMQTAA DKCEEMEEGY TQCSQFLYGV QEKGIMNKG  
 1001 VIYALWDYEP QNDDELPME GDCMTIIHRE DEDEIEWWA RLNDKEGYVP  
 == =====

1051 RNLLGLYPR1 KPRQRSLA  
 HITS AT: 1029-1037

REFERENCE 1: 138:316493

L4 ANSWER 9 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 514228-34-3 REGISTRY  
 CN Protein NOV20a (human) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 61: PN: WO03031571 SEQID: 62 claimed protein  
 CI MAN  
 SQL 1005

SEQ 1 MDLTLAELQE MASRQQQQIE AQQQLLATKE QRLKFLKQD QRQQQQVAEQQ  
 51 EKLKRLKEIA ENQEAKLKKV RALKGHVEQK RLSNGKLVEE IEQMNNLFQOQ  
 101 KQRELVLAVS KVEELTRQLE MLKNGRIDSHH HDNQSAVAEL DRLYKELQLR  
 151 NKLNQEQNAKL LQQRECLNK RNSEVAVMDK RVNELRDRRLW KKKAALQQKE  
 201 NLPVSSDGNL PQQAASAPSR VAAVGPYIQS STMPRMPSRP ELLVKPALPD

251 GSLVIQASEG PMKIQTLPNM RSGAASQTKG SKIHPVGPDW SPSNADLFPS  
 301 QGSASVPQST GNALDQVDDG EVPLREKEKK VRPFMSMFDAV DQSNAPPSSFG  
 351 TLRKNQSSED ILRDAQVANK NVAKVPPPVP TKPKQINLPY FGQTNQPPSD  
 401 IKPDGSSQQL STVVPMSGTK PKPAGQQPRV LLSPSIPPSVG QDQTLSPGSK  
 451 QESPPAAAVR PFTPQPSKDT LLPPFRKPQT VAASSIYSMY TQQQAPGKNF  
 501 QQAVQSAALK THTRGPHFSS VYGKPVIAAA QNQQQHOPENI YSNSQGKPGS  
 551 PEPETEPVSS VQENHENERI PRPLSPTKLL PFLSNPYRNQ SDADLEALRK  
 601 KLSNAPRPLK KRSSITEPEG PNGPNIQKLL YQRTTIAAME TISVPSYPSK  
 651 SASVTASSES PVEIQNPYIHL VEPEKEVDSL VPESLSPEDV GNASTENSDM  
 701 PAPSPGLDYE PEGVPDNPSPN LQNNPEEPNP EAPHVLDVYL EYPPYPPPP  
 751 YPSGEPEGPG EDSVSMRPPPE ITGQVSLPPG KRTNLRKTGS ERIAHGMRVK  
 801 FNPLALLDS SLEGEFDLQ RIIYEVDDPS LPNDEGITAL HNAVCAGHTE  
 851 IVKFLVQFGV NVNAADSDGW TPLHCAASCN NVQVCKFLVE SGAAVFAMTY  
 901 SDMQTAADKC EEMEEGYTQC SQFLYGVQEK MGIMNKGVIY ALWDYEPQND  
 951 DELPMKEGDC MTIIHREDED EIEWWWARLN DKEGYVPRNL LGLYPRIKPR

===== =====

1001 QRSLA  
HITS AT: 966-974

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 138:316493

L4 ANSWER 10 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 497259-83-3 REGISTRY  
 CN L-Tryptophan, L-arginyl-L- $\alpha$ -glutamyl-L- $\alpha$ -aspartyl-L- $\alpha$ -  
 glutamyl-L- $\alpha$ -aspartyl-L- $\alpha$ -glutamyl-L-isoleucyl-L- $\alpha$ -  
 glutamyl- (9CI) (CA INDEX NAME)  
 SQL 9

SEQ 1 REDEDEIEW  
=====

HITS AT: 1-9

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 140:104698

REFERENCE 2: 138:166255

L4 ANSWER 11 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 479014-21-6 REGISTRY  
 CN Protein p53BP2 (p53-binding protein 2) (human) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 3: PN: US20020197243 SEQID: 2 claimed protein  
 CI MAN  
 SQL 1005

SEQ 1 MDLTLAELQE MASRQQQQIE AQQQLLATKE QRLKFLKQD QRQQQQVAEQ  
 51 EKLKRLKEIA ENQEAKLKKV RALKGHVEQK RLSNGKLVEE IEQMNLFQQ  
 101 KQRELVLAVS KVEELTRQLE MLKNGRIDSH HDNQSAVAEL DRLYKELQLR  
 151 NKLNQEQQNAK LQQQRECLNK RNSEVAVMDK RVNELRDRRLW KKAAALQQKE  
 201 NLPVSSDGNL PQQQASAPSR VAAVGPYIQS STMPRMPSRP ELLVKPALPD  
 251 GSLVIQASEG PMKIQTLPNM RSGAASQTKG SKIHPVGPDW SPSNADLFPS  
 301 QGSASVPQST GNALDQVDDG EVPLREKEKK VRPFMSMFDAV DQSNAPPSSFG  
 351 TLRKNQSSED ILRDAQVANK NVAKVPPPVP TKPKQINLPY FGQTNQPPSD

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401 IKPDGSSQQL STVVPSMGT PKPAGQQPRV LLSPSIPSVG QDQTLSPGSK
451 QESPPAAAVR PFTPQPSKDT LLPPFRKPQT VAASSIYSMY TQQQAPGKNF
501 QQAVQSLALK THTRGPHFSS VYGKPVIAAA QNQQQHPENI YSNSQGKPGS
551 PEPETEPVSS VQENHENERI PRPLSPTKLL PFLSNPYRNQ SDADLEALRK
601 KLSNAPRPLK KRSSITEPEG PNGPNIQKLL YQRTTIAAME TISVPSYPSK
651 SASVTASSES PVEIQNPYIHL VEPEKEVVSL VPESLSPEDV GNASTENSDM
701 PAPSPGLDYE PEGVPDNSPN LQNNPEEPNP EAPHVLDVYL EYPPYPPPP
751 YPSGEPEGPG EDSVSMRPPE ITGQVSLPPG KRTNLRKTGS ERIAHGMRVK
801 FNPLALLLDS SLEGEFDLVQ RIIYEVDDPS LPNDEGITAL HNAVCAGHTE
851 IVKFLVQFGV NVNAADSDGW TPLHCAASCN NVQVCKFLVE SGAAVFAMTY
901 SDMQTAADKC EEMEEGYTQC SQFLYGVQEK MGIMNKGVIY ALWDYEPQND
951 DELPMKEGDC MTIIHREDED EIEWWWARLN DKEGYVPRNL LGLYPRIKPR
===== =====

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1001 QRSLA  
HITS AT: 966-974

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 138:49915

L4 ANSWER 12 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 469356-94-3 REGISTRY  
 CN Protein p53BP2 (p53-binding protein) (human) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN 2: PN: WO02078609 SEQID: 2 claimed protein  
 CI MAN  
 SQL 1005

```

SEQ      1 MDLTLAELQE MASRQQQQIE AQQQLLATKE QRLKFLKQQD QRQQQQVAEQ
      51 EKLKRLKEIA ENQEAKLKKV RALKGHVEQK RLSNGKLVEE IEQMNLLFQQ
      101 KQRELVLAWS KVEELTRQLE MLKNGRIDSH HDNQSAVAEL DRLYKELQLR
      151 NKLNEQNAK LQQQRECLNK RNSEAVMDK RVNELRDRlw KKAAALQQKE
      201 NLPVSSDGNL PQQAAASAPSR VAAVGPYIQS STMPMRMPSRP ELLVKPALPD
      251 GSLVIQASEG PMKIQTLPNM RSGAASQTKG SKIHPVGPDW SPSNADLFPS
      301 QGSASVPQST GNALDQVDDG EVPLREKEKK VRPFMSMFDAV DQSNAPPSFG
      351 TLRKNQSSED IILRDAQVANK NVAKVPPPVP TKPKQINLPY FGQTNQPPSD
      401 IKPDGSSQQL STVVPSMGT PKPAGQQPRV LLSPSIPSVG QDQTLSPGSK
      451 QESPPAAAVR PFTPQPSKDT LLPPFRKPQT VAASSIYSMY TQQQAPGKNF
      501 QQAVQSLALK THTRGPHFSS VYGKPVIAAA QNQQQHPENI YSNSQGKPGS
      551 PEPETEPVSS VQENHENERI PRPLSPTKLL PFLSNPYRNQ SDADLEALRK
      601 KLSNAPRPLK KRSSITEPEG PNGPNIQKLL YQRTTIAAME TISVPSYPSK
      651 SASVTASSES PVEIQNPYIHL VEPEKEVVSL VPESLSPEDV GNASTENSDM
      701 PAPSPGLDYE PEGVPDNSPN LQNNPEEPNP EAPHVLDVYL EYPPYPPPP
      751 YPSGEPEGPG EDSVSMRPPE ITGQVSLPPG KRTNLRKTGS ERIAHGMRVK
      801 FNPLALLLDS SLEGEFDLVQ RIIYEVDDPS LPNDEGITAL HNAVCAGHTE
      851 IVKFLVQFGV NVNAADSDGW TPLHCAASCN NVQVCKFLVE SGAAVFAMTY
      901 SDMQTAADKC EEMEEGYTQC SQFLYGVQEK MGIMNKGVIY ALWDYEPQND
      951 DELPMKEGDC MTIIHREDED EIEWWWARLN DKEGYVPRNL LGLYPRIKPR
===== =====

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1001 QRSLA  
HITS AT: 966-974

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 137:293524

L4 ANSWER 13 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 389661-99-8 REGISTRY  
 CN transcription factor ASPP2 (apoptosis-stimulating protein of p53 2) (human  
 gene ASPP2) (9CI) (CA INDEX NAME)  
 OTHER NAMES:  
 CN ASPP2 protein (human gene ASPP2)  
 CN GenBank CAC83012  
 CN GenBank CAC83012 (Translated from: GenBank AJ318888)  
 CI MAN  
 SQL 1128

SEQ 1 MMPMFLTVYL SNNEQHFTEV PVTPETICRD VVDLCKEPGE SDCHLAEVWC  
 51 GSERPVADNE RMFDVLQRFQ SQRNEVRFFL RHERPPGRDI VSGPRSQDPS  
 101 LKRNGVKVPG EYRRKENGVN SPRMDLTLAE LQEMASRQQQ QIEAQQQLLA  
 151 TKEQRALKFLK QDQDQQQQV AEQEKLKLK EIAENQEAKL KKVRALKGHV  
 201 EQKRLSNGKL VEEIEQMNLN FQQKQRELVL AVSKVEELTR QLEMILKNGRI  
 251 DSHHDNQSAV AELDRLYKEL QLRNKLNQEQQ NAKLQQQREC LNKRNSEVAV  
 301 MDKRVNELRD RLWKKKAALQ QKENLPVSSD GNLPQQAASA PSRVAAVGPy  
 351 IQSSTMPMRMP SRPELLVKPA LPDGSLSVIQA SEGPMKIQTL PNMRSGAASQ  
 401 TKGSKIHPVG PDWSPSNADL FPSQGSASVP QSTGNALDQV DDGEVPLREK  
 451 EKKVRPFSMF DAVDQSNAPP SFGTLRKNSQ SEDILRDAQV ANKNAVKPP  
 501 PVPTPKQIN LPYFGQTNQP PSDIKPDGSS QQLSTVVPSM GTKPKPAGQQ  
 551 PRVLLSPSIP SVGQDQTLSP GSKQESPPAA AVRPFPTQPS KDTLLPPFRK  
 601 PQTVAAASSI SMYTQQQAPG KNFQQAVQSA LTKTHTRGP FSSVYGKPVI  
 651 AAAAQNQQQHP ENIYSNSQGK PGSPEPETEP VSSVQENHEN ERIPRPLSPT  
 701 KLLPFLSNPY RNQSDADLEA LRKKLNSNAPR PLKKRSSITE PEGPNGPNIQ  
 751 KLLYQRTTIA AMETISVPSY PSKSASVTAS SESPVETIQNP YLHVEPEKEV  
 801 VSLVPESLSP EDVGNASTEN SDMPAPSPGL DYEPEGVPDN SPNLQNNPEE  
 851 PNPEAPHVLD VYLEEYPPY PPPYPPSGEPE GPGEDSVSMR PPEITGQVSL  
 901 PPGKRTNLRK TGSERIAHGM RVKFNPLALL LDSSLEGEDF LVQRIIYEV  
 951 DPSLPNDEGI TALHNACVAG HTEIVKFLVQ FG NVNVAADS DGWTPLHCAA  
 1001 SCNNVQVCKF LVEGAFAVTA MYTSDMQTAA DKCEEMEEGY TQCSQFLYGV  
 1051 QEKGIMNKG VIYALWDYEP QNDDELPKME GDCMTIIHRE DEDEIEWWA  
 == =====

1101 RLNDKEGYVP RNLLGLYPRI KPRQRSLA  
 HITS AT: 1089-1097

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 136:116397

L4 ANSWER 14 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN  
 RN 355485-67-5 REGISTRY  
 CN Protein (human clone 53BP2 p53-binding C-terminal fragment) (9CI) (CA  
 INDEX NAME)  
 CI MAN  
 SQL 529

SEQ 1 KPQTVAAASSI YSMYTQQQAP GKNFQQAVQSL ALTKTHTRGP HFSSVYGKPV  
 51 IAAAQNQQQH PENIYSNSQG KPGSPEPETE PVSSVQENHE NERIPRPLSP  
 101 TKLLPFLSNP YRNQSDADLE ALRKKLSNAP RPLKKRSSIT EPEGPNGPNI  
 151 QKLLYQRTTIA AAMETISVPSY YPSKSASVTAS SSES PVETIQN PYLHVEPEKE  
 201 VVSLVPESLP PEDVGNASTEN NSDMPAPSPGL LDYEPEGVPD NSPNLQNNPE  
 251 EPNPEAPHVLD DVYLEEYPPY PPPYPPSGEPE EPGGEDSVSM RPPEITGQVS  
 301 LPPGKRTNLRK KTGSERIAHGM MRVKFNPLAL LLDSSLEGEDF DLVQRIIYEV  
 351 DDPSLPNDEG ITALHNACVAG HTEIVKFLVQ FG NVNVAADS DGWTPLHCAA

401 ASCNNVQVCK FLVESGAAVF AMTYSDMQTA ADKCEEMEEG YTQCSQFLYG  
 451 VQEKGIMNK GVIYALWDYE PQNDDELPMK EGDCMTIIHR EDEDEIEWWW

= =====

501 ARLNDKEGYV PRNLLGLYPR IKPRQRSLA

HITS AT: 490-498

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 135:193985

REFERENCE 2: 135:190398

L4 ANSWER 15 OF 15 REGISTRY COPYRIGHT 2005 ACS on STN

RN 178967-19-6 REGISTRY

CN bcl-2 protein (human p53-binding reduced) (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 2098: PN: W003095618 TABLE: 1 claimed protein

CN 290: PN: W003010336 TABLE: 1B claimed protein

CN 3040: PN: W003038130 FIGURE: 3 claimed protein

CN 3493: PN: W003091391 FIGURE: 20 unclaimed protein

CN 569: PN: W02004038376 TABLE: 5 unclaimed protein

CN 635: PN: W003091391 FIGURE: 19 unclaimed protein

CN Bbp/53BP2 (human cell line HAL-01; B-cell progenitor cell line gene  
 BBP/53BP2)

CN GenBank AAC50557

CN GenBank AAC50557 (Translated from: GenBank U58334)

CN Protein Bcl2 (human p53-binding reduced)

CI MAN

SQL 1005

SEQ 1 MDLTLAELQE MASRQQQQIE AQQQLLATKE QRLKFLKQQD QRQQQQVAEQ

51 EKLKRLKEIA ENQEAKLKVK RALKGHVEQK RLSNGKLVEE IEQMNNLFQQ

101 KQRELVLAWS KVEELTRQLE MLKNGRIDSH HDNQSAVAEL DRLYKELQLR

151 NKLNQEQQNAK LQQQRECLNK RNSEAVMDK RVNELRDRlw KKKAALQQKE

201 NLPVSSDGNL PQQAAASAPSR VAAVGPYIQS STMPMRPSRP ELLVKPALPD

251 GSLVIQASEG PMKIQTLPNM RSGAASQTKG SKIHPVGPDW SPSNADLFPS

301 QGSASVPQST GNALDQVDDG EVPLREKEKK VRPFMSMFDAV DQSNAPPSFG

351 TLRKNQSSED IILRDAQVANK NVAKVPVPV TKPKQINLPY FGQTNQPPSD

401 IKPDGSSQQL STVVPSMGTK PKPAGQQPRV LLSPSIPPSVG QDQTLSPGSK

451 QESPPAAAVR PFTPQPSKDT LLPPFRKPQT VAASSIYSMY TQQQAPGKNF

501 QQAVQSQLTK THTRGPHFSS VYGKPVIAAA QNQQQHOPENI YSNSQGKPGS

551 PEPETEPVSS VQENHENERI PRPLSPTKLL PFLSNPYRNQ SDADLEALRK

601 KLSNAPRPLK KRSSITEPEG PNGPNIQKLL YQRTTIAAME TISVPSYPSK

651 SASVTASSES PVEIQNPYLY VEPEKEVVSL VPESLSPEDV GNASTENSDM

701 PAPSPGLDYE PEGVPDNSPN LQNNPEEPNP EAPHVLDVYL EYPPYPPPPP

751 YPSGEPEGPG EDSVSMRPPE ITGQVSLPPG KRTNLRKTGS ERIAHGMRVK

801 FNPLALLLDS SLEGEFDLVQ RIIYEVDDPS LPNDEGITAL HNAVCAHTE

851 IVKFLVQFGV NVNAADSDGW TPLHCAASCN NVQVCKFLVE SGAAVFAMTY

901 SDMQTAADKC EEMEEGYTQC SQFLYGVQEK MGIMNKGVIIY ALWDYEPQND

951 DELPMKEGDC MTIIHREDED EIEWWWARLN DKEGYVPRNL LGLYPRIKPR

=====

1001 QRSLA

HITS AT: 966-974

\*\*RELATED SEQUENCES AVAILABLE WITH SEQLINK\*\*

REFERENCE 1: 140:420388

REFERENCE 2: 140:40262

REFERENCE 3: 139:379453

REFERENCE 4: 139:363045

REFERENCE 5: 138:380506

REFERENCE 6: 138:164674

REFERENCE 7: 125:106785

(FILE 'MEDLINE, BIOSIS, EMBASE, CANCERLIT' ENTERED AT 15:05:31 ON 03 MAR 2005)

L5 0 S L4

(FILE 'CAPLUS' ENTERED AT 15:05:50 ON 03 MAR 2005)

L6 86 SEA FILE=CAPLUS ABB=ON PLU=ON R175H OR G245S OR R248Q OR R249S OR R273H OR R282W OR I195T

L7 83 SEA FILE=CAPLUS ABB=ON PLU=ON L6(S) (MUTAT? OR MUTANT OR MUTAGEN? OR POLYMORPH?)

L8 71 SEA FILE=CAPLUS ABB=ON PLU=ON L7 AND P53

L9 22 SEA FILE=CAPLUS ABB=ON PLU=ON L8 AND (STABIL? OR STABLE?)

-key terms  
Claim 26

L10 21 L9 NOT L2

L10 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 25 Oct 2004

ACCESSION NUMBER: 2004:884446 CAPLUS

DOCUMENT NUMBER: 141:360334

TITLE: CP-31398 Restores DNA-binding Activity to Mutant p53 in Vitro but Does Not Affect p53 Homologs p63 and p73

AUTHOR(S): Demma, Mark J.; Wong, Serena; Maxwell, Eugene; Dasmahapatra, Bimalendu

CORPORATE SOURCE: Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA

SOURCE: Journal of Biological Chemistry (2004), 279(44), 45887-45896

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The p53 protein plays a major role in the maintenance of genome stability in mammalian cells. Mutations of p53 occur in over 50% of all cancers and are indicative of highly aggressive cancers that are hard to treat. Recently, there has been a high degree of interest in therapeutic approaches to restore growth suppression functions to mutant p53. Several compds. have been reported to restore wild type function to mutant p53. One such compound, CP-31398, has been shown effective in vivo, but questions have arisen to whether it actually affects p53. Here we show that mutant p53,

isolated from cells treated with CP-31398, is capable of binding to p53 response elements in vitro. We also show the compound restores DNA-binding activity to mutant p53 in cells as determined by a chromatin immunoprecipitation assay. In addition, using purified p53 core domain from two different hotspot mutants (R273H and R249S), we show that CP-31398 can restore DNA-binding activity in a dose-dependent manner. Using a quant. DNA binding assay, we also show that CP-31398 increases significantly the amount of mutant p53 that binds to cognate DNA (Bmax) and its affinity (Kd) for DNA. The compound, however, does not affect the affinity (Kd value) of wild type p53 for DNA and only increases Bmax slightly. In a similar assay PRIMA1 does not have any effect on p53 core DNA-binding activity. We also show that CP-31398 had no effect on the DNA-binding activity of p53 homologs p63 and p73.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 13 May 2004  
 ACCESSION NUMBER: 2004:386272 CAPLUS  
 DOCUMENT NUMBER: 141:420098  
 TITLE: Mutant p53 expression enhances drug resistance in a hepatocellular carcinoma cell line  
 AUTHOR(S): Chan, Kin-Tak; Lung, Maria Li  
 CORPORATE SOURCE: Department of Biology, The Hong Kong University of Science and Technology, Hong Kong (SAR), Peop. Rep. China  
 SOURCE: Cancer Chemotherapy and Pharmacology (2004), 53(6), 519-526  
 CODEN: CCPHDZ; ISSN: 0344-5704  
 PUBLISHER: Springer-Verlag  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Chemoresistance is a major problem in the treatment of hepatocellular carcinoma. Certain p53 mutants may enhance drug resistance in cancer cells. To determine whether two frequently occurring p53 mutants, R248Q and R273C, would increase the drug resistance of liver cancer cells, stable cell lines expressing these specific p53 mutants were established by transfecting the p53-null Hep3B cells with mutant p53 expression vectors, and then treating them with the anticancer drugs doxorubicin and paclitaxel. The cells expressing the p53 mutant, R248Q, but not R273C, displayed cross-resistance to both drugs, in contrast to the control cells expressing the vector alone. Moreover, both the expression and the activity of the multiple drug resistance gene product, P-glycoprotein, were elevated in p53 mutant R248Q-expressing cells. Reduced uptake of doxorubicin was also observed in the R248Q-expressing cells. These results suggest that expression of the p53 mutant, R248Q, in liver cancer cells may enhance their drug resistance and that upregulation of P-glycoprotein activity may contribute to this protective effect.  
 REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 25 Mar 2004  
 ACCESSION NUMBER: 2004:245726 CAPLUS  
 DOCUMENT NUMBER: 140:401217  
 TITLE: Mutant **p53** exerts a dominant negative effect by preventing wild-type **p53** from binding to the promoter of its target genes  
 AUTHOR(S): Willis, Amy; Jung, Eun Joo; Wakefield, Therese; Chen, Xinbin  
 CORPORATE SOURCE: Department of Cell Biology and UAB Comprehensive Cancer Center, The University of Alabama at Birmingham, Birmingham, AL, 35294-0005, USA  
 SOURCE: Oncogene (2004), 23(13), 2330-2338  
 CODEN: ONCNES; ISSN: 0950-9232  
 PUBLISHER: Nature Publishing Group  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Mutation of the **p53** tumor suppressor gene is the most common genetic alteration in human cancer. A majority of these mutations are missense mutations in the DNA-binding domain. As a result, the mutated **p53** gene encodes a full-length protein incapable of transactivating its target genes. In addition to this loss of function, mutant **p53** can have a dominant neg. effect over wild-type **p53** and/or gain of function activity independently of the wild-type protein. To better understand the nature of the tumorigenic activity of mutant **p53**, we have investigated the mechanism by which mutant **p53** can exert a dominant neg. effect. We have established several **stable** cell lines capable of inducibly expressing a **p53** mutant alone, wild-type **p53** alone, or both proteins concurrently. In this context, we have used chromatin immunopptn. to determine the ability of wild-type **p53** to bind to its endogenous target genes in the presence of various **p53** mutants. We have found that **p53** missense mutants markedly reduce the binding of wild-type **p53** to the **p53** responsive element in the target genes of p21, MDM2, and PIG3. These findings correlate with the reduced ability of wild-type **p53** in inducing these and other endogenous target genes and growth suppression in the presence of mutant **p53**. We also showed that mutant **p53** suppresses the ability of wild-type **p53** in inducing cell cycle arrest. This highlights the sensitivity and utility of the dual inducible expression system because in previous studies, **p53**-mediated cell cycle arrest is not affected by transiently overexpressed **p53** mutants. Together, our data showed that mutant **p53** exerts its dominant neg. activity by abrogating the DNA binding, and subsequently the growth suppression, functions of wild-type **p53**.  
 REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 22 Dec 2003  
 ACCESSION NUMBER: 2003:992974 CAPLUS  
 DOCUMENT NUMBER: 140:57487  
 TITLE: **p53** hot-spot mutants are resistant to ubiquitin-independent degradation by increased binding to NAD(P)H:Quinone oxidoreductase 1  
 AUTHOR(S): Asher, Gad; Lotem, Joseph; Tsvetkov, Peter; Reiss, Veronica; Sachs, Leo; Shaul, Yosef

CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, 76100, Israel  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(25), 15065-15070  
 CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Proteasomal degradation of **p53** is mediated by two alternative pathways that are either dependent or independent of both Mdm2 and ubiquitin. The ubiquitin-independent pathway is regulated by NAD(P)H: quinone oxidoreductase 1 (NQO1) that **stabilizes p53**. The NQO1 inhibitor dicoumarol induces ubiquitin-independent **p53** degradation. We now show that, like dicoumarol, several other coumarin and flavone inhibitors of NQO1 activity, which compete with NAD(P)H for binding to NQO1, induced ubiquitin-independent **p53** degradation and inhibited wild-type **p53**-mediated apoptosis. Although wild-type **p53** and several **p53** mutants were sensitive to dicoumarol-induced degradation, the most frequent "hot-spot" **p53** mutants in human cancer, **R175H**, **R248H**, and **R273H**, were resistant to dicoumarol-induced degradation, but remained sensitive to

Mdm2-ubiquitin-mediated degradation. The two alternative pathways for **p53** degradation thus have different **p53** structural requirements. Further mutational anal. showed that arginines at positions 175 and 248 were essential for dicoumarol-induced **p53** degradation. NQO1 bound to wild-type **p53** and dicoumarol, which induced a conformational change in NQO1, inhibited this binding. Compared with wild-type **p53**, the hot-spot **p53** mutants showed increased binding to NQO1, which can explain their resistance to dicoumarol-induced degradation. NQO1 thus has an important role in **stabilizing hot-spot p53** mutant proteins in human cancer.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 27 Nov 2003

ACCESSION NUMBER: 2003:926529 CAPLUS

DOCUMENT NUMBER: 140:57472

TITLE: Elevated levels of prostate-specific antigen (PSA) in prostate cancer cells expressing mutant **p53** is associated with tumor metastasis

AUTHOR(S): Downing, Sean; Bumak, Clare; Nixdorf, Sheri; Ow, Kim; Russell, Pamela; Jackson, Paul

CORPORATE SOURCE: Oncology Research Centre, Prince of Wales Hospital, Randwick, Australia

SOURCE: Molecular Carcinogenesis (2003), 38(3), 130-140  
 CODEN: MOCAE8; ISSN: 0899-1987

PUBLISHER: Wiley-Liss, Inc.  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The underlying basis for rising levels of prostate-specific antigen (PSA) in prostate cancer is not fully understood, but attention has turned to the possibility that loss of normal **p53** function might be directly involved. We have investigated the relationship between

**p53** function and PSA expression using in vitro and in vivo approaches. Three prostate cancer-derived **p53** mutants (F134L, M237L, R273H) were introduced into LNCaP prostate cancer cells and stable transfectants established. Expression of mutant **p53** was demonstrated by Western blot anal., inactivation of wt**p53** function, and a loss of **p53**-dependent responses to DNA damage induced by UV-irradiation and cisplatin. Levels of PSA mRNA and secreted protein were determined by RT-PCR and Western blotting, resp.

## Serine

protease activity was assessed using an esterase assay. In vivo effects of mutant **p53** expression were examined after orthotopic implantation into prostates of nude mice. Expression of all **p53** mutants was associated with elevated PSA mRNA and secreted PSA protein. In

a

representative line, mutant **p53** was also associated with increased PSA protease-like activity compared with a control line expressing wildtype **p53**. Overall PSA levels, and PSA levels in serum from mice bearing tumors derived from cells expressing mutant **p53**, were increased compared with levels in mice bearing tumors derived from control cells. In addition, the tumors derived from cells with mutant **p53** had increased vascularization and induced lymph node metastases. These data provide in vitro and in vivo support for the notion that **p53** mutations directly contribute to increased levels of serum PSA, and are associated with more aggressive tumors.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 01 Oct 2003  
 ACCESSION NUMBER: 2003:766871 CAPLUS  
 DOCUMENT NUMBER: 139:347259  
 TITLE: Conversion of Wild-type **p53** Core Domain into a Conformation that Mimics a Hot-spot Mutant  
 AUTHOR(S): Ishimaru, Daniella; Maia, Lenize F.; Maiolino, Larissa M.; Quesado, Pablo A.; Lopez, Priscila C. M.; Almeida, Fabio C. L.; Valente, Ana Paula; Silva, Jerson L.  
 CORPORATE SOURCE: Instituto de Ciencias Biomedicas, Centro Nacional de Ressonancia Magnetica Nuclear de Macromoleculas, Departamento de Bioquimica Medica, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, 21941-590, Brazil  
 SOURCE: Journal of Molecular Biology (2003), 333(2), 443-451  
 CODEN: JMOBAK; ISSN: 0022-2836  
 PUBLISHER: Elsevier  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The wild-type **p53** protein can be driven into a conformation corresponding to that adopted by structural mutant forms by heterodimerization with a mutant subunit. To seek partially folded states of the wild-type **p53** core domain (p53C) we used high hydrostatic pressure (HP) and subzero temps. Aggregation of the protein was observed in parallel with its pressure denaturation at 25 and 37°. However, when HP expts. were performed at 4°, the extent of denaturation and aggregation was significantly less pronounced. On the other hand, subzero temps. under pressure led to cold denaturation and yielded a non-aggregated, alternative conformation of p53C. NMR (1H15N-NMR) data

showed that the alternative p53C conformation resembled that of the hot-spot oncogenic **mutant R248Q**. This alternative state was as susceptible to denaturation and aggregation as the **mutant R248Q** when subjected to HP at 25°.

Together these data demonstrate that wild-type p53C adopts an alternative conformation with a mutant-like **stability**, consistent with the dominant-neg. effect caused by many mutants. This alternative conformation is likely related to inactive forms that appear *in vivo*, usually driven by interaction with mutant proteins. Therefore, it can be a valuable target in the search for ways to interfere with protein misfolding and hence to prevent tumor development.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 23 Jun 2003  
 ACCESSION NUMBER: 2003:478413 CAPLUS  
 DOCUMENT NUMBER: 139:241840  
 TITLE: Kinetic Instability of **p53** Core Domain  
 Mutants: Implications For Rescue By Small Molecules  
 Friedler, Assaf; Veprintsev, Dmitry B.; Hansson, Lars  
 O.; Fersht, Alan R.  
 CORPORATE SOURCE: Cambridge Centre for Protein Engineering, Medical  
 Research Council Centre, Cambridge University Chemical  
 Laboratory, Cambridge, CB2 2QH, UK  
 SOURCE: Journal of Biological Chemistry (2003), 278(26),  
 24108-24112  
 CODEN: JBCHA3; ISSN: 0021-9258  
 PUBLISHER: American Society for Biochemistry and Molecular  
 Biology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Oncogenic mutations in the tumor suppressor protein **p53** are  
 found mainly in its DNA-binding core domain. Many of these mutants are  
 thermodynamically unstable at body temperature. Here the authors show that  
 these

mutants also denature within minutes at 37°. The half-life ( $t_{1/2}$ ) of the unfolding of wild-type **p53** core domain was 9 min. Hot spot mutants denatured more rapidly with increasing thermodn. instability. The highly destabilized **mutant I195T** had a  $t_{1/2}$  of less than 1 min. The wild-type **p53**-(94-360) construct, containing the core and tetramerization domains, was more **stable**, with  $t_{1/2}$  = 37 min at 37°, similar to full-length **p53**. After unfolding, the denatured proteins aggregated, the rate increasing with higher concns. of protein. A derivative of the **p53**-stabilizing peptide CDB3 significantly slowed down the unfolding rate of the **p53** core domain. Drugs such as CDB3, which rescue the conformation of unstable mutants of **p53**, have to act during or immediately after biosynthesis. They should maintain the mutant protein in a folded conformation and prevent its aggregation, allowing it enough time to reach the nucleus and bind its sequence-specific target DNA or the **p53** binding proteins that will stabilize it.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 04 Jun 2003  
 ACCESSION NUMBER: 2003:425714 CAPLUS  
 DOCUMENT NUMBER: 140:159220  
 TITLE: Rescuing the conformation of mutant **p53** core domain  
 AUTHOR(S): Friedler, Assaf; Hansson, Lars O.; Veprintsev, Dmitry B.; Freund, Stefan M. V.; Rippin, Thomas M.; Fersht, Alan R.  
 CORPORATE SOURCE: MRC Centre, Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, Cambridge, CB2 2QH, UK  
 SOURCE: Innovation and Perspectives in Solid Phase Synthesis & Combinatorial Libraries: Peptides, Proteins and Nucleic Acids--Small Molecule Organic Chemistry Diversity, Collected Papers, International Symposium, 7th, Southampton, United Kingdom, Sept. 18-22, 2001 (2002), Meeting Date 2001, 115-118. Editor(s): Epton, Roger. Mayflower Worldwide Ltd.: Kingswinford, UK.  
 CODEN: 69DYT7; ISBN: 0-9515735-4-3  
 DOCUMENT TYPE: Conference  
 LANGUAGE: English  
 AB Mutations in the tumor suppressor protein **p53** can, in principle, be rescued using a small mol. that binds the native, but not the denatured state. The equilibrium is then shifted towards the native state, resulting in **stabilization** and restoration of activity. The feasibility of this concept was demonstrated using peptides such as 9 amino acid residue peptide, CDB3, that binds to **p53** core domain and **stabilizes** it in vitro. Based on the crystal structure of the complex between **p53** and its binding protein 53BP2, the peptides derived from the three 53BP2 loops that bind **p53** core domain were designed and synthesized. In addition, peptides from the C-terminal and proline-rich domains of **p53**, which were suggested to bind the core domain, were synthesized. CDB3, as a peptide that globally **stabilizes** **p53** core domain, could restore DNA binding activity to the globally destabilized **mutant I195T**. Results showed that short peptides can be used to **stabilize** **mutant p53** and restore its DNA binding activity. CDB3 binds at the DNA binding site, but DNA binds **p53** tighter and thus can displace the peptide. CDB3 acts in the following mechanism: it binds globally destabilized mutants that are unable to bind DNA, and brings them to the stage where they can bind DNA, then DNA displaces the peptide and binds to the newly refolded mutant.  
 REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 02 Feb 2003  
 ACCESSION NUMBER: 2003:77898 CAPLUS  
 DOCUMENT NUMBER: 138:233667  
 TITLE: Structure, Function, and Aggregation of the Zinc-Free Form of the **p53** DNA Binding Domain  
 AUTHOR(S): Butler, James S.; Loh, Stewart N.  
 CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, State University of New York Upstate Medical

SOURCE: University, Syracuse, NY, 13210, USA  
 Biochemistry (2003), 42(8), 2396-2403  
 CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The **p53** DNA binding domain (DBD) contains a single bound zinc ion that is essential for activity. Zinc remains bound to wild-type DBD at temps. below 30°; however, it rapidly dissocs. at physiol. temperature. The resulting zinc-free protein (apoDBD) is folded and **stable**. NMR spectra reveal that the DNA binding surface is altered in the absence of Zn<sup>2+</sup>. Fluorescence anisotropy studies show that Zn<sup>2+</sup> removal abolishes site-specific DNA binding activity, although full nonspecific DNA binding affinity is retained. Surprisingly, the majority of tumorigenic mutations that destabilize DBD do not appreciably destabilize apoDBD. The **R175H mutation** instead substantially accelerates the rate of Zn<sup>2+</sup> loss. A considerable fraction of cellular **p53** may therefore exist in the folded zinc-free form, especially when tumorigenic mutations are present. ApoDBD appears to promote aggregation of zinc-bound DBD via a nucleation-growth process. These data provide an explanation for the dominant neg. phenotype exhibited by many mutations. Through a combination of induced **p53** aggregation and diminished site-specific DNA binding activity, Zn<sup>2+</sup> loss may represent a significant inactivation pathway for **p53** in the cell.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 29 Apr 2002  
 ACCESSION NUMBER: 2002:317812 CAPLUS  
 DOCUMENT NUMBER: 137:165125  
 TITLE: Factors governing loss and rescue of DNA binding upon single and double mutations in the **p53** core domain  
 AUTHOR(S): Wright, Jon D.; Noskov, Sergey Yu; Lim, Carmay  
 CORPORATE SOURCE: Institute of Biomedical Sciences, Academia Sinica, Taipei, 11529, Taiwan  
 SOURCE: Nucleic Acids Research (2002), 30(7), 1563-1574  
 CODEN: NARHAD; ISSN: 0305-1048  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The mutation of R273H in the **p53** core domain (**p53**-CD) is one of the most common mutations found in human cancers. Although the 273H **p53**-CD retains the wild-type conformation and **stability**, it lacks sequence-specific DNA binding, a transactivation function and growth suppression. However, mutating T284→R in the 273H **p53**-CD restores the DNA binding affinity, and transactivation and tumor suppressor functions. Since X-ray/NMR structures of DNA-free or DNA-bound mutant **p53**-CD mols. are unavailable, the factors governing the loss and rescue of sequence-specific DNA binding in the 273H and 273H+284R **p53**-CD, resp., are unclear. Hence, we have carried out mol. dynamics (MD) simulations of the wild-type, single mutant and double mutant **p53**-CD, free and DNA bound, in the presence of explicit water mols. Based on the MD structures, the DNA-binding free energy of each **p53** mol.

has been computed and decomposed into component energies and contributions from the interface residues. The wild-type and mutant **p53**-CD MD structures were found to be consistent with the antibody-binding, X-ray and NMR data. The predicted DNA binding affinity and specificity of both mutant **p53**-CDs were also in accord with exptl. data. The non-detectable DNA binding of the 273H **p53**-CD is due mainly to the disruption of a hydrogen-bonding network involving R273, D281 and R280, leading to a loss of major groove binding by R280 and K120. The restoration of DNA binding affinity and specificity of the 273H+284R **p53**-CD is due mainly to the introduction of another DNA-binding site at position 284, leading to a recovery of major groove binding by R280 and K120. The important role of water mols. and the DNA major groove conformation as well as implications for structure-based linker rescue of the 273H **p53**-CD DNA-binding affinity are discussed.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 22 Apr 2002  
 ACCESSION NUMBER: 2002:298460 CAPLUS  
 DOCUMENT NUMBER: 137:210559  
 TITLE: Characterization of the **p53**-rescue drug  
 CP-31398 in vitro and in living cells  
 AUTHOR(S): Rippin, Thomas M.; Bykov, Vladimir J. N.; Freund,  
 Stefan M. V.; Selivanova, Galina; Wiman, Klas G.;  
 Fersht, Alan R.  
 CORPORATE SOURCE: MRC Centre, Cambridge University Chemical Laboratory  
 and Cambridge Center for Protein Engineering,  
 Cambridge, CB2 2QH, UK  
 SOURCE: Oncogene (2002), 21(14), 2119-2129  
 CODEN: ONCNES; ISSN: 0950-9232  
 PUBLISHER: Nature Publishing Group  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB The Pfizer compound CP-31398 has been reported to **stabilize** the  
 core domain of the tumor suppressor **p53** in vitro and be an  
 effective anti-cancer drug by virtue of rescuing destabilized mutants of  
**p53**. The authors did not detect any interaction between the  
**p53** core domain and CP-31398 in vitro by a wide range of quant.  
 biophys. techniques over a wide range of conditions. CP-31398 did not  
**stabilize** **p53** in the authors' expts. However, the  
 authors found that CP-31398 intercalated with DNA and also altered and  
 destabilized the DNA-**p53** core domain complex. The authors  
 analyzed by NMR TROSY the interaction of the domain with a DNA oligomer  
 and identified the changes in the complex on the binding of CP-31398.  
 CP-31398 also decreased sequence-specific DNA binding of wild-type  
**p53** and His 273 mutant **p53**. CP-31398 had a non-specific  
 toxic effect independent of mutant **p53** expression in several  
 cell lines carrying Tet-regulated mutant **p53**. CP-31398 caused a  
 small increase in MDM-2 expression and a more pronounced **p53**  
 -independent increase in Bax expression. CP-31398 did, however, induce  
 the PAb1620 epitope (characteristic of native **p53**) in cells  
 expressing His 175 mutant **p53**. This was prevented by  
 cycloheximide, suggesting that any **stabilizing** action of  
 CP-31398 would have to be on newly synthesized **p53**. One of the  
 unstable **mutants** that was reported to have been rescued by

CP-31398, R249S, does not bind DNA when folded at lower temps.  
 REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 15 Feb 2002  
 ACCESSION NUMBER: 2002:121133 CAPLUS  
 DOCUMENT NUMBER: 136:292597  
 TITLE: A peptide that binds and **stabilizes**  
**p53** core domain: chaperone strategy for rescue  
 of oncogenic mutants  
 AUTHOR(S): Friedler, Assaf; Hansson, Lars O.; Veprintsev, Dmitry  
 B.; Freund, Stefan M. V.; Rippin, Thomas M.; Nikolova,  
 Penka V.; Proctor, Mark R.; Rudiger, Stefan; Fersht,  
 Alan R.  
 CORPORATE SOURCE: Medical Research Council Centre, Cambridge University  
 Chemical Laboratory and Cambridge Centre for Protein  
 Engineering, Cambridge, CB2 2QH, UK  
 SOURCE: Proceedings of the National Academy of Sciences of the  
 United States of America (2002), 99(2), 937-942  
 CODEN: PNASA6; ISSN: 0027-8424  
 PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Conformationally compromised oncogenic mutants of the tumor suppressor  
 protein **p53** can, in principle, be rescued by small mols. that  
 bind the native, but not the denatured state. We describe a strategy for  
 the rational search for such mols. A nine-residue peptide, CDB3, which  
 was derived from a **p53** binding protein, binds to **p53**  
 core domain and **stabilizes** it in vitro. NMR studies showed that  
 CDB3 bound to **p53** at the edge of the DNA binding site, partly  
 overlapping it. The fluorescein-labeled peptide, FL-CDB3, binds wild-type  
**p53** core domain with a dissociation constant of 0.5  $\mu$ M, and raises  
 the apparent melting temps. of wild-type and a representative oncogenic  
 mutant, R249S core domain, gadd45 DNA competes with CDB3 and displaces it  
 from its binding site. But this competition does not preclude CDB3 from  
 being a lead compound. CDB3 may act as a "chaperone" that maintains existing  
 or newly synthesized destabilized **p53** mutants in a native  
 conformation and then allows transfer to specific DNA, which binds more  
 tightly. Indeed, CDB3 restored specific DNA binding activity to a highly  
 destabilized **mutant I195T** to close to that of  
 wild-type level.  
 REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 09 Jul 2001  
 ACCESSION NUMBER: 2001:493520 CAPLUS  
 DOCUMENT NUMBER: 136:241188  
 TITLE: Various forms of mutant **p53** confer  
 sensitivity to cisplatin and doxorubicin in bladder  
 cancer cells  
 AUTHOR(S): Chang, Fu-Lin; Lai, Ming-Derg  
 CORPORATE SOURCE: Department of Biochemistry, College of Medicine,  
 National Cheng Kung University and Department of  
 Industrial Safety and Hygiene, Chung Hwa Institute of

SOURCE: Technology, Tainan, Taiwan  
Journal of Urology (Hagerstown, MD, United States)  
(2001), 166(1), 304-310

PUBLISHER: Lippincott Williams & Wilkins  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Purposes: The nature of **p53** mutation has been reported to affect cellular responses to chemotherapy. We characterized the impact of **p53** mutations on drug resistance in bladder cancer cells.  
 Materials and Methods: Various human **p53** mutants (V143A, V173L, H179Q, N247I and **R273H**) were introduced to the TCC-SUP bladder carcinoma cell line to establish **stable** transfectants. The expression of mutant **p53** was demonstrated by reverse transcriptase-polymerase chain reaction and immunocytochem. anal. The sensitivity to cisplatin and doxorubicin in these transfectants was determined by trypan blue exclusion. Cell death mediated by cisplatin and doxorubicin was characterized by terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling anal., Hoechst 33258 staining and annexin-V binding assay. Results: The expression of all forms of mutant **p53** protein except p53His273 enhanced sensitivity to cisplatin and doxorubicin. The chemosensitivity of p53His273 transfectants is similar to that of parental TCC-SUP and control transfectants. Cisplatin induced cell death undergoes apoptosis, as demonstrated by Hoechst staining, annexin-V assay and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling, resp. In contrast, doxorubicin induced cell death probably occurs through a non-apoptotic pathway. Conclusions: These results indicated that the nature of **p53** mutations may effect the cellular response to anticancer drugs and many forms of mutant **p53** protein may enhance chemosensitivity through apoptotic or non-apoptotic pathways in bladder cancer cells.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 28 Jun 2001  
 ACCESSION NUMBER: 2001:465094 CAPLUS  
 DOCUMENT NUMBER: 135:193334  
 TITLE: ZBP-89 promotes growth arrest through stabilization of **p53**  
 AUTHOR(S): Bai, Longchuan; Merchant, Juanita L.  
 CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA  
 SOURCE: Molecular and Cellular Biology (2001), 21(14), 4670-4683

PUBLISHER: American Society for Microbiology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB Transcription factor **p53** can induce growth arrest and/or apoptosis in cells through activation or repression of downstream target genes. Recently, we reported that ZBP-89 cooperates with histone acetyltransferase coactivator p300 in the regulation of p21waf1, a cyclin-dependent kinase inhibitor whose associated gene is a target gene of **p53**. Therefore, we examined whether ZBP-89 might also inhibit cell

growth by activating p53. In the present study, we demonstrate that elevated levels of ZBP-89 induce growth arrest and apoptosis in human gastrointestinal cell lines. The ZBP-89 protein accumulated within 4 h, and the p53 protein accumulated within 16 h, of serum starvation without changes in p14ARF levels, demonstrating a physiol. increase in the cellular levels of these two proteins. Overexpression of ZBP-89 stabilized the p53 protein and enhanced its transcriptional activity through direct protein-protein interactions. The DNA binding and C-terminal domains of p53 and the zinc finger domain of ZBP-89 mediated the interaction. A point mutation in the p53 DNA binding domain, R273H, greatly reduced ZBP-89-mediated stabilization but not their phys. interaction. Furthermore, ZBP-89 formed a complex with p53 and MDM2 and therefore did not prevent the MDM2-p53 interaction. However, heterokaryon assays demonstrated that ZBP-89 retained p53 in the nucleus. Collectively, these data indicate that ZBP-89 regulates cell proliferation in part through its ability to directly bind the p53 protein and retard its nuclear export. Our findings further our understanding of how ZBP-89 modulates cell proliferation and reveals a novel mechanism by which the p53 protein is stabilized

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 07 Mar 2001  
 ACCESSION NUMBER: 2001:160241 CAPLUS  
 DOCUMENT NUMBER: 135:222217  
 TITLE: p73 is transcriptionally regulated by DNA damage, p53, and p73  
 AUTHOR(S): Chen, Xinbin; Zheng, Yiman; Zhu, Jianhui; Jiang, Jieyuan; Wang, Jian  
 CORPORATE SOURCE: Institute of Molecular Medicine and Genetics, Medical College of Georgia, Augusta, GA, 30912, USA  
 SOURCE: Oncogene (2001), 20(6), 769-774  
 CODEN: ONCNES; ISSN: 0950-9232  
 PUBLISHER: Nature Publishing Group  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB P73 is a member of the p53 family. Recent studies have shown that DNA damage can stabilize p73 protein and enhance p73-mediated apoptosis in a c-Abl dependent manner. To determine what regulates p73 transcriptionally, we analyzed the expression of p73 in several cell lines following genotoxic stresses. We found that p73 is induced in certain cell lines when treated with therapeutic DNA damaging agents. We also found that p53 and p73, but not mutant p53 (R249S) and p73 $\beta$ 292, directly induce the expression of the p73 gene. In addition, we found one potential p53-binding site in the promoter of the p73 gene. This binding site is responsive to p53, p73, and DNA damage. Taken together, these data suggest that p73 is transcriptionally regulated by DNA damage and p53, and is autoregulated.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN

ED Entered STN: 27 Feb 2001  
 ACCESSION NUMBER: 2001:141119 CAPLUS  
 DOCUMENT NUMBER: 134:308356  
 TITLE: p53 associates with and targets ΔNp63  
 into a protein degradation pathway  
 AUTHOR(S): Ratovitski, Edward A.; Paturajan, Meera; Hibi, Kenji;  
 Trink, Barry; Yamaguchi, Kengo; Sidransky, David  
 CORPORATE SOURCE: Department of Otolaryngology-Head and Neck Surgery,  
 Division of Head and Neck Cancer Research, The Johns  
 Hopkins University School of Medicine, Baltimore, MD,  
 21205-2196, USA  
 SOURCE: Proceedings of the National Academy of Sciences of the  
 United States of America (2001), 98(4), 1817-1822  
 CODEN: PNASA6; ISSN: 0027-8424  
 PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB A human p53 homolog, p63 (p40/p51/p73L/CUSP) that maps to the  
 chromosomal region 3q27-29 was found to produce a variety of transcripts  
 that encode DNA-binding proteins with and without a trans-activation  
 domain (TA- or ΔN-, resp.). The p63 gene locus was amplified in  
 squamous cell carcinoma, and overexpression of ΔNp63 (p40) led to  
 increased growth of transformed cells in vitro and in vivo. Moreover,  
 p63-null mice displayed abnormal epithelial development and germ-line  
 human mutations were found to cause ectodermal dysplasia. The authors now  
 demonstrate that certain p63 isoforms form complexes with p53.  
 p53 mutations R175H or R248W abolish the  
 association of p53 with p63, whereas V143A or R273H has no  
 effect. Deletion studies suggest that the DNA-binding domains of both  
 p53 and p63 mediate the association. Overexpression of wild type but  
 not mutant (R175H) p53 results in the  
 caspase-dependent degradation of certain ΔNp63 proteins (p40 and  
 ΔNp63α). The association between p53 and ΔNp63  
 supports a previously unrecognized role for p53 in regulation of  
 ΔNp63 stability. The ability of p53 to mediate  
 ΔNp63 degradation may balance the capacity of ΔNp63 to accelerate  
 tumorigenesis or to induce epithelial proliferation.  
 REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS  
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 13 Feb 2000  
 ACCESSION NUMBER: 2000:100300 CAPLUS  
 DOCUMENT NUMBER: 132:235186  
 TITLE: Mechanism of rescue of common p53 cancer  
 mutations by second-site suppressor mutations  
 AUTHOR(S): Nikolova, Penka V.; Wong, Kam-Bo; DeDecker, Brian;  
 Henckel, Julia; Fersht, Alan R.  
 CORPORATE SOURCE: Cambridge University Chemical Laboratory and Cambridge  
 Centre for Protein Engineering, MRC Centre, Cambridge,  
 CB2 2QH, UK  
 SOURCE: EMBO Journal (2000), 19(3), 370-378  
 CODEN: EMJODG; ISSN: 0261-4189  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English

AB The core domain of **p53** is extremely susceptible to mutations that lead to loss of function. We analyzed the **stability** and DNA-binding activity of such mutants to understand the mechanism of second-site suppressor mutations. Double-mutant cycles show that N239Y and N268D act as "global **stability**" suppressors by increasing the **stability** of the cancer mutants **G245S** and V143A-the free energy changes are additive. Conversely, the suppressor H168R is specific for the **R249S** mutation: despite destabilizing wild type, H168R has virtually no effect on the **stability** of **R249S**, but restores its binding affinity for the **gadd45** promoter. NMR structural comparisons of R249S/H168R and R249S/T123A/H168R with wild type and R249S show that H168R reverts some of the structural changes induced by R249S. These results have implications for possible drug therapy to restore the function of tumorigenic mutants of **p53**: the function of mutants such as V143A and **G245S** is theor. possible to restore by small mols. that simply bind to and hence stabilize the native structure, whereas **R249S** requires alteration of its **mutant** native structure.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 14 May 1999  
 ACCESSION NUMBER: 1999:298113 CAPLUS  
 DOCUMENT NUMBER: 131:156276  
 TITLE: Modulation of wild-type **p53** activity by mutant **p53** **R273H** depends on the **p53** responsive element (p53RE). A comparative study between the p53REs of the MDM2, WAF1/Cip1 and Bax genes in the lung cancer environment  
 AUTHOR(S): Zacharatos, P. V.; Gorgoulis, V. G.; Kotsinas, A.; Manolis, E. N.; Liloglou, T.; Rassidakis, A. N.; Kanavaros, P.; Field, J. D.; Halazonetis, T.; Kittas, Ch.  
 CORPORATE SOURCE: Department of Histology and Embryology, School of Medicine, University of Athens, Athens, Greece  
 SOURCE: Anticancer Research (1999), 19(1A), 579-588  
 CODEN: ANTRD4; ISSN: 0250-7005  
 PUBLISHER: International Institute of Anticancer Research  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Wild-type (weight) **p53** is a tumor-suppressor protein which acts via transcriptional and transcriptional-independent mechanisms. The transcriptional function of **p53** is mediated by specific responsive elements (REs). The MDM2, WAF1/Cip1, and Bax genes possess p53REs and their activation by wt **p53** induces cell cycle progression, arrest, and programmed cell death (apoptosis), resp. Mutations of the **p53** gene are detected in more than 50% of the human malignant tumors. **p53** mutants seem to have a more **stable** conformation and are suggested to exert dominant-neg. inhibition of wt **p53** in cells containing both wt and mutant (mt) alleles. However, recent studies show that certain mt **p53** proteins possess a "gain of function" phenotype. In the present study, the effects of the second most-frequent **p53** mutant **R273H** on the p53REs of the MDM2, WAF1/Cip1, and Bax genes in the

H1299 non-small-cell lung carcinoma cell line were examined. Although mt p53 R273H alone was unable to bind and transactivate the corresponding p53REs, it enhanced the MDM2-p53RE-mediated gene transcription of wt p53 (pos.-dominant effect) and prevented the wt p53 transactivation of the p53REs of WAF1/Cip1 and Bax genes (neg.-dominant effect). Apparently, in the appropriate environment, differential transcription of critical p53 target genes by certain p53 mutant proteins may illustrate another mechanism implicated in tumor development.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 11 May 1998  
 ACCESSION NUMBER: 1998:266241 CAPLUS  
 DOCUMENT NUMBER: 129:37195  
 TITLE: Adenovirus type 12-induced fragility of the human RNU2 locus requires p53 function  
 AUTHOR(S): Li, Zengji; Yu, Adong; Weiner, Alan M.  
 CORPORATE SOURCE: Departments of Molecular Biophysics and Biochemistry and of Genetics, Yale University, New Haven, CT, 06520-8114, USA  
 SOURCE: Journal of Virology (1998), 72(5), 4183-4191  
 CODEN: JOVIAM; ISSN: 0022-538X  
 PUBLISHER: American Society for Microbiology  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Adenovirus type 12 (Ad12) infection of human cells induces four chromosomal fragile sites corresponding to the U1 small nuclear RNA (snRNA) genes (the RNU1 locus), the U2 snRNA genes (RNU2), the U1 snRNA pseudogenes (PSU1), and the 5S rRNA genes (RN5S). Ad12-induced fragility of the RNU2 locus requires U2 snRNA transcriptional regulatory elements and viral early functions but not viral replication or integration, or chromosomal sequences flanking the RNU2 locus. We now show that Ad12 cannot induce the RNU1, RNU2, or PSU1 fragile sites in Saos-2 cells lacking the p53 and retinoblastoma (Rb) proteins but viral induction of fragility is rescued in these cells when the expression of wild-type p53 or selected hot-spot mutants (i.e., V143A, R175H, R248W, and R273H) is restored by transient expression or stable retroviral transduction. We also observed weak constitutive fragility of the RNU1 and RNU2 loci in cells belonging to xeroderma pigmentosum complementation groups B and D (XPB and XPD) which are partially defective in the ERCC2 (XPD) and ERCC3 (XPB) helicase activities shared between the recomplexome and the RNA polymerase II basal transcription factor TFIID. We propose a model for Ad12-induced chromosome fragility in which interaction of p53 with the Ad12 E1B 55-kDa transforming protein (and possibly E4orf6) induces a p53 gain of function which ultimately perturbs the RNA polymerase II basal transcription apparatus. The p53 gain of function could interfere with chromatin condensation either by blocking mitotic shutdown of U1 and U2 mRNA transcription or by phenocopying global or local DNA damage. Specific fragilization of the RNU1, RNU2, and PSU1 loci could reflect the usually high local concentration of strong transcription units or the specialized nature of the U1 and U2 snRNA transcription apparatus  
 REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 02 May 1998  
 ACCESSION NUMBER: 1998:249758 CAPLUS  
 DOCUMENT NUMBER: 129:23853  
 TITLE: Genetic selection of intragenic suppressor mutations that reverse the effect of common **p53** cancer mutations  
 AUTHOR(S): Brachmann, Rainer K.; Yu, Kexin; Eby, Yolanda; Pavletich, Nikola P.; Boeke, Jef D.  
 CORPORATE SOURCE: Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA  
 SOURCE: EMBO Journal (1998), 17(7), 1847-1859  
 CODEN: EMJODG; ISSN: 0261-4189  
 PUBLISHER: Oxford University Press  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Several lines of evidence suggest that the presence of the wild-type tumor suppressor gene **p53** in human cancers correlates well with successful anti-cancer therapy. Restoration of wild-type **p53** function to cancer cells that have lost it might therefore improve treatment outcomes. Using a systematic yeast genetic approach, we selected second-site suppressor mutations that can overcome the deleterious effects of common **p53** cancer mutations in human cells. We identified several suppressor mutations for the **V143A**, **G245S** and **R249S** cancer mutations. The beneficial effects of these suppressor mutations were demonstrated using mammalian reporter gene and apoptosis assays. Further expts. showed that these suppressor mutations could override addnl. **p53** cancer mutations. The mechanisms of such suppressor mutations can be elucidated by structural studies, ultimately leading to a framework for the discovery of small mols. able to stabilize **p53** mutants.  
 REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2005 ACS on STN  
 ED Entered STN: 17 Jan 1998  
 ACCESSION NUMBER: 1998:26794 CAPLUS  
 DOCUMENT NUMBER: 128:126436  
 TITLE: Thermodynamic stability of wild-type and mutant **p53** core domain  
 AUTHOR(S): Bullock, Alex N.; Henckel, Julia; DeDecker, Brian S.; Johnson, Christopher M.; Nikolova, Penka V.; Proctor, Mark R.; Lane, David P.; Fersht, Alan R.  
 CORPORATE SOURCE: Medical Research Council Centre, Cambridge University Chemical Laboratory, Cambridge, CB2 2QH, UK  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1997), 94(26), 14338-14342  
 CODEN: PNASA6; ISSN: 0027-8424  
 PUBLISHER: National Academy of Sciences  
 DOCUMENT TYPE: Journal  
 LANGUAGE: English  
 AB Some 50% of human cancers are associated with mutations in the core domain of

the tumor suppressor **p53**. Many mutations are thought just to destabilize the protein. To assess this and the possibility of rescue, the authors have set up a system to analyze the **stability** of the core domain and its mutants. The use of differential scanning colorimetry or spectroscopy to measure its melting temperature leads to irreversible denaturation and aggregation and so is useful as only a qual. guide to **stability**. There are excellent two-state denaturation curves on the addition of urea that may be analyzed quant. One Zn<sup>2+</sup> ion remains tightly bound in the holoform of **p53** throughout the denaturation curve. The **stability** of wild type is 6.0 kcal (1 kcal = 4.18 kJ)/mol at 25° and 9.8 kcal/mol at 10°. The oncogenic mutants **R175H**, **C242S**, **R248Q**, **R249S**, and **R273H** are destabilized by 3.0, 2.9, 1.9, 1.9, and 0.4 kcal/mol, resp. Under certain denaturing conditions, the wild-type domain forms an aggregate that is relatively highly fluorescent at 340 nm on excitation at 280 nm. The destabilized mutants give this fluorescence under milder denaturation conditions.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 15:10:34 ON 03 MAR 2005)

L11 92 S L9  
L12 24 DUP REM L11 (68 DUPLICATES REMOVED)

L12 ANSWER 1 OF 24 MEDLINE on STN DUPLICATE 1  
ACCESSION NUMBER: 2004531006 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 15308639  
TITLE: CP-31398 restores DNA-binding activity to mutant  
p53 in vitro but does not affect p53  
homologs p63 and p73.  
AUTHOR: Demma Mark J; Wong Serena; Maxwell Eugene; Dasmahapatra  
Bimalendu  
CORPORATE SOURCE: Schering-Plough Research Institute, Kenilworth, New Jersey  
07033, USA.  
SOURCE: Journal of biological chemistry, (2004 Oct 29) 279 (44)  
45887-96. Electronic Publication: 2004-08-11.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200411  
ENTRY DATE: Entered STN: 20041026  
Last Updated on STN: 20041219  
Entered Medline: 20041130

AB The **p53** protein plays a major role in the maintenance of genome **stability** in mammalian cells. Mutations of **p53** occur in over 50% of all cancers and are indicative of highly aggressive cancers that are hard to treat. Recently, there has been a high degree of interest in therapeutic approaches to restore growth suppression functions to mutant **p53**. Several compounds have been reported to restore wild type function to mutant **p53**. One such compound, CP-31398, has been shown effective in vivo, but questions have arisen to whether it actually affects **p53**. Here we show that mutant **p53**, isolated from cells treated with CP-31398, is capable of binding to

**p53** response elements in vitro. We also show the compound restores DNA-binding activity to mutant **p53** in cells as determined by a chromatin immunoprecipitation assay. In addition, using purified **p53** core domain from two different hotspot mutants (**R273H** and **R249S**), we show that CP-31398 can restore DNA-binding activity in a dose-dependent manner. Using a quantitative DNA binding assay, we also show that CP-31398 increases significantly the amount of mutant **p53** that binds to cognate DNA ( $B(\max)$ ) and its affinity ( $K(d)$ ) for DNA. The compound, however, does not affect the affinity ( $K(d)$  value) of wild type **p53** for DNA and only increases  $B(\max)$  slightly. In a similar assay PRIMA1 does not have any effect on **p53** core DNA-binding activity. We also show that CP-31398 had no effect on the DNA-binding activity of **p53** homologs p63 and p73.

L12 ANSWER 2 OF 24 MEDLINE on STN DUPLICATE 2  
 ACCESSION NUMBER: 2004239635 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 15004724  
 TITLE: Mutant **p53** expression enhances drug resistance in a hepatocellular carcinoma cell line.  
 AUTHOR: Chan Kin-Tak; Lung Maria Li  
 CORPORATE SOURCE: Department of Biology, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong (SAR), People's Republic of China.  
 SOURCE: Cancer chemotherapy and pharmacology, (2004 Jun) 53 (6) 519-26. Electronic Publication: 2004-03-04.  
 Journal code: 7806519. ISSN: 0344-5704.  
 PUB. COUNTRY: Germany: Germany, Federal Republic of  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200406  
 ENTRY DATE: Entered STN: 20040513  
 Last Updated on STN: 20040629  
 Entered Medline: 20040628  
 AB Chemoresistance is a major problem in the treatment of hepatocellular carcinoma. Certain **p53** mutants may enhance drug resistance in cancer cells. To determine whether two frequently occurring **p53** mutants, **R248Q** and **R273C**, would increase the drug resistance of liver cancer cells, stable cell lines expressing these specific **p53** mutants were established by transfecting the **p53**-null Hep3B cells with mutant **p53** expression vectors, and then treating them with the anticancer drugs doxorubicin and paclitaxel. The cells expressing the **p53** mutant, **R248Q**, but not **R273C**, displayed cross-resistance to both drugs, in contrast to the control cells expressing the vector alone. Moreover, both the expression and the activity of the multiple drug resistance gene product, P-glycoprotein, were elevated in **p53** mutant **R248Q**-expressing cells. Reduced uptake of doxorubicin was also observed in the **R248Q**-expressing cells. These results suggest that expression of the **p53** mutant, **R248Q**, in liver cancer cells may enhance their drug resistance and that upregulation of P-glycoprotein activity may contribute to this protective effect.

L12 ANSWER 3 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-663348 [62] WPIDS  
 DOC. NO. CPI: C2003-180150  
 TITLE: Nucleic acid molecule encoding tumor suppressor protein, useful for treating cancer, comprises intragenic suppressor mutation suppressing mutation of transcription factor in human cancers when the mutations are in a cis configuration.  
 DERWENT CLASS: B04  
 INVENTOR(S): BRACHMANN, R K  
 PATENT ASSIGNEE(S): (UNIW) UNIV WASHINGTON  
 COUNTRY COUNT: 102  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003061603	A2	20030731 (200362)*	EN	27	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003206373	A1	20030902 (200422)			

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003061603	A2	WO 2003-US24	20030115
AU 2003206373	A1	AU 2003-206373	20030115

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003206373	A1 Based on	WO 2003061603

PRIORITY APPLN. INFO: US 2002-348394P 20020116

AN 2003-663348 [62] WPIDS

AB WO2003061603 A UPAB: 20031001

NOVELTY - A nucleic acid molecule (A1) encoding human transcription factor and tumor suppressor protein (p53) comprises at least one intragenic suppressor mutation capable of suppressing a mutation of human p53, which occurs in human cancers when the intragenic suppressor and cancer mutations are present in a cis configuration.

DETAILED DESCRIPTION - A nucleic acid molecule (A1) encoding human p53 comprises at least one intragenic suppressor mutation capable of suppressing a mutation of human p53 which occurs in human cancers when the intragenic suppressor and cancer mutations are present in a cis configuration. The intragenic suppressor mutation is T81S, A83V, P87R, Q100L, Q100R, Q104P, F113L, L114V, T118M, V122I, C124S, K139R, Q144L, W146R, Q165L, V172I, H178Y, S183T, A189V, F212L, E224G, S227P, S227T, D228N, D228A, D228E, C229W, T230S, T231I, I232V, H233R, H233Y, Y234F, N235K, N235S, Y236N, N239M, N239W, N239L, N239F, N239R, N239H, S240Q, S240T, S240R, D281G, E285G, E285K, E294G, G325R, E343V, E346G

and/or D352G.

INDEPENDENT CLAIMS are also included for:

(1) A nucleic acid molecule (B1) encoding human **p53** comprises a set of at least one intragenic suppressor mutation, capable of suppressing a mutation of human **p53** which occurs in human cancers when the intragenic suppressor and cancer mutations are present in a *cis* configuration. The set is selected from F113L, L114V+T123P+V172I+A189V, T123P+A189V, S227P+N239Y, T118M+H168R, V122I+C124S+H168R, T123A+H168R, K139R+H168R+N239Y, H168R+T231I, T123A+S240R, H178Y+S240R, D281G+E285G+G325R+E343V, E285K+D352G, E285K+E294G+E346G, T81S+A83V+S240R, P87R+Q100L+Q104P+Q144L+S240R, Q100R+W146R+S240R, Q165L+F212L+S240R, S183T+S240R, E224G+S240R, S240R, D228A+N235K+N239M, D228E+N235K+Y236N+N239L, I232V+H233R+Y234F+N235K+N239L, N235K+S240T, Y234F+N239L, N235K+N239R, H233Y+N239Y, N239F, N239Y+S240Q, H233Y+N235K+N239Y, N235K+N239Y, N235S+N239Y+S240N, D228N+N239Y, N235K+N239W, D228E+N239Y, N235K+S240N, N239W, T230S+N239Y, S227T+N235K+N239Y, H233R+N235S+N239R+S240R, N239R, N239R+S240R, C229W+N239R+S240R, N239L+S240R, N239F+S240R, I232V+N239H+S240R, D228E+C229W+N235K+ N239Y+S240R and/or N239Y+S240R;

(2) A human **p53** protein comprising the intragenic suppressor mutation or the set comprising at least one intragenic suppressor mutation;

(3) A cell comprising (A1), (B1) or human **p53** protein; and

(4) A human **p53** polypeptide comprising a portion of human **p53** protein comprising residues 94-292, and at least one of the intragenic suppressor mutation or the set of the intragenic suppressor mutations.

ACTIVITY - Cytostatic; Gene therapy.

No biological data available.

MECHANISM OF ACTION - None given.

USE - The nucleic acids encapsulated or carried into vectors are used in gene therapy for the treatment of cancer. The **p53** molecules or polypeptides are used as cancer therapeutics, and for protein crystallography to determine a protein **stabilization** mechanism.

ADVANTAGE - The **p53** suppressor mutations are resistant to the dominant-negative effect of **p53** cancer mutants, and are efficient in inducing cell cycle arrest and apoptosis for the treatment of cancer.

Dwg.0/3

L12 ANSWER 4 OF 24 WPIDS COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-256537 [25] WPIDS

DOC. NO. NON-CPI: N2003-203483

DOC. NO. CPI: C2003-066578

TITLE: Novel **stabilizing** molecule which binds to a site that partially overlaps a functional site of polypeptide and **stabilizes** native state of polypeptide, but not denatured state of polypeptide, useful for treating cancer.

DERWENT CLASS: B04 D16 S03

INVENTOR(S): FERSHT, A; FRIEDLER, A

PATENT ASSIGNEE(S): (MEDI-N) MEDICAL RES COUNCIL

COUNTRY COUNT: 102

PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG
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Searcher : Shears 571-272-2528

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WO 2003014144 A2 20030220 (200325)\* EN 73  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU  
 MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA  
 ZM ZW  
 EP 1414846 A2 20040506 (200430) EN  
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC  
 MK NL PT RO SE SI SK TR  
 AU 2002319540 A1 20030224 (200461)  
 US 2005008653 A1 20050113 (200506)

## APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003014144	A2	WO 2002-GB3668	20020809
EP 1414846	A2	EP 2002-749128	20020809
		WO 2002-GB3668	20020809
AU 2002319540	A1	AU 2002-319540	20020809
US 2005008653	A1 CIP of	WO 2002-GB3668	20020809
		US 2004-775679	20040210

## FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1414846	A2 Based on	WO 2003014144
AU 2002319540	A1 Based on	WO 2003014144

PRIORITY APPLN. INFO: GB 2002-10740 20020510; GB  
 2001-19557 20010810; GB  
 2001-27917 20011121

AN 2003-256537 [25] WPIDS  
 AB WO2003014144 A UPAB: 20030416

NOVELTY - A **stabilizing** molecule (I) which binds to and stabilizes the native state of a polypeptide, but not a denatured state of the polypeptide, in which the **stabilizing** molecule binds to a site which at least partially overlaps a functional site of the polypeptide, and in which the **stabilizing** molecule does not consist of a natural binding partner of the polypeptide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) identifying (I) capable of **stabilizing** a polypeptide in which the polypeptide may be reversibly denatured so that it exists in a native state and a denatured state, comprising:

(a) providing a native state of the polypeptide comprising a functional site;

(b) exposing the polypeptide to a candidate **stabilizing** molecule;

(c) selecting a candidate **stabilizing** molecule which binds to the site which at least partially overlaps a functional site of the native state of the polypeptide; and

(d) determining whether the binding **stabilizes** the native

state of the polypeptide; or

(2) identifying (I) capable of **stabilizing** a polypeptide in which the polypeptide may be reversibly denatured so that it exists in a native state and a denatured state, comprising:

(a) identifying a functional site of the polypeptide;

(b) providing the polypeptide fragment comprising the functional site;

(c) selecting a candidate **stabilizing** molecule which binds to the polypeptide fragment at a site which at least partially overlaps a functional site; and

(d) determining whether the selected candidate **stabilizing** molecule **stabilizes** a native state of a polypeptide;

(3) a **stabilizing** molecule capable of **stabilizing** the polypeptide, identified by the method of (2); and

(4) a pharmaceutical composition comprising (I), together with a carrier, diluent or excipient.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Apoptosis inducer.

The apoptosis-inducing effects of FL-CD3 on cell cycle was tested. Tumor cells were treated with 10 micro g/ml of peptide and the cell cycle distribution and cell death (as subG1 fraction) 24 hours post treatment was analyzed using fluorescence activated cell sorting (FACS) analysis. The percentage of dead cells was determined by trypan blue exclusion, the number of dead cells in H1299-His175 cells before treatment was 5 %, after treatment 37 %; in control H1299 (**p53**-), before 3 % after treatment 11 %; in Saos-2 His273 cells, before 3 %, after 28 %; in control Saos-2(**p53**-), before treatment 3 %, after 13 %. From the results of this experiment, it was clear that CDB3 peptide induced apoptosis in tumor cells in **p53**-dependent manner. There was difference between **p53**-positive and **p53**-negative cells.

Surprisingly, no growth arrest was detected.

USE - (I) is useful for **stabilizing** the native state of a polypeptide which is reversibly denatured so that it exists in a native state and a denatured state, in which the **stabilizing** molecule does not bind to the polypeptide in its denatured state. (I) is useful for increasing the concentration of a native state of a reversibly denatured polypeptide in a system which comprises a polypeptide in a first native state and a second denatured state, which involves providing (I) which binds to the polypeptide at a site which at least partially overlaps with a functional site in the first native state and thereby **stabilizing** the first native state of the polypeptide, and allowing the **stabilizing** molecule to bind to the polypeptide.

(I) is also useful for restoring a wild type phenotype of an organism comprising a mutation in a polypeptide, in which the mutation leads to denaturation of the polypeptide and a mutant phenotype, which involves exposing the organism or its part to (I). (I) is useful for treating a disease in a patient, caused by or associated with a mutation in a polypeptide which leads to denaturation of the polypeptide. (I) is not a natural binding partner of the polypeptide, and consists of fragment of natural binding partner of the polypeptide. (I) is a polypeptide engineered to include a polypeptide binding domain, preferably a binding loop, of a natural binding partner of the polypeptide. (I) is exposed to polypeptide or the system in presence of a natural binding partner of the polypeptide. The affinity of binding between **stabilizing** molecule and the polypeptide or site is less than the affinity of a natural binding partner of the polypeptide and the polypeptide or the

binding site. The binding between the **stabilizing** molecule and the binding site **stabilizes** the polypeptide to enable binding between the polypeptide and the natural binding partner, and the binding between the polypeptide and the natural binding partner **stabilizes** the native state of the polypeptide. (I) is also useful for assisting the binding between a polypeptide and a natural binding partner of the polypeptide, which involves **stabilizing** a native state of the polypeptide, and exposing the **stabilized** polypeptide to the natural binding partner; and for assisting the binding between a polypeptide and a first molecule, in which the polypeptide exists in a native state and a denatured state, which involves providing a second **stabilizing** molecule capable of binding to a site which at least partially overlaps a functional site in the native state of the polypeptide, allowing the second **stabilizing** molecule to bind to the polypeptide to form a complex and thereby **stabilizing** the native state of the polypeptide, exposing the polypeptide and bound second **stabilizing** molecule complex to the first molecule, and allowing the first molecule to bind to the polypeptide, and thereby displacing the second **stabilizing** molecule. The functional site comprises or at least partially overlaps with a structural domain, a protein binding domain, a nucleic acid binding domain or an active site of an enzyme. The functional site is essential to the structure or activity, or both, of the polypeptide. The polypeptide comprises an oncogenic protein or a tumor suppressor protein such as **p53**. (I) is useful for treating a disease, or in the manufacture of a medicament for treating the disease, e.g. cancer. (I) is also useful for inducing the onset or progression of apoptosis in one or more cells. (I) is useful for preparing a medicament for inducing the onset or progression of apoptosis in one or more cells. (All claimed.)

ADVANTAGE - (I) does not bind to the denatured/inactive form of the polypeptide, thus preferentially **stabilizing** the active conformation. (I) is capable of increasing the relative concentration of a native form of the polypeptide as compared to the a denatured form.

Dwg.0/10

L12 ANSWER 5 OF 24	MEDLINE on STN	DUPPLICATE 3
ACCESSION NUMBER:	2003292121	MEDLINE
DOCUMENT NUMBER:	PubMed ID: 12700230	
TITLE:	Kinetic instability of <b>p53</b> core domain mutants: implications for rescue by small molecules.	
AUTHOR:	Friedler Assaf; Veprintsev Dmitry B; Hansson Lars O; Fersht Alan R	
CORPORATE SOURCE:	Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, Medical Research Council Centre, Hills Road, Cambridge CB2 2QH, United Kingdom.	
SOURCE:	Journal of biological chemistry, (2003 Jun 27) 278 (26) 24108-12. Electronic Publication: 2003-04-16. Journal code: 2985121R. ISSN: 0021-9258.	
PUB. COUNTRY:	United States	
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE)	
LANGUAGE:	English	
FILE SEGMENT:	Priority Journals	
ENTRY MONTH:	200308	
ENTRY DATE:	Entered STN: 20030624 Last Updated on STN: 20030821 Entered Medline: 20030820	

AB Oncogenic mutations in the tumor suppressor protein **p53** are found mainly in its DNA-binding core domain. Many of these mutants are thermodynamically unstable at body temperature. Here we show that these mutants also denature within minutes at 37 degrees C. The half-life ( $t(1/2)$ ) of the unfolding of wild-type **p53** core domain was 9 min. Hot spot mutants denatured more rapidly with increasing thermodynamic instability. The highly destabilized **mutant I195T** had a  $t(1/2)$  of less than 1 min. The wild-type **p53** -(94-360) construct, containing the core and tetramerization domains, was more **stable**, with  $t(1/2) = 37$  min at 37 degrees C, similar to full-length **p53**. After unfolding, the denatured proteins aggregated, the rate increasing with higher concentrations of protein. A derivative of the **p53-stabilizing** peptide CDB3 significantly slowed down the unfolding rate of the **p53** core domain. Drugs such as CDB3, which rescue the conformation of unstable mutants of **p53**, have to act during or immediately after biosynthesis. They should maintain the mutant protein in a folded conformation and prevent its aggregation, allowing it enough time to reach the nucleus and bind its sequence-specific target DNA or the **p53** binding proteins that will **stabilize** it.

L12 ANSWER 6 OF 24 MEDLINE on STN DUPLICATE 4  
 ACCESSION NUMBER: 2003585060 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14634213  
 TITLE: **p53** hot-spot mutants are resistant to ubiquitin-independent degradation by increased binding to NAD(P)H:quinone oxidoreductase 1.  
 AUTHOR: Asher Gad; Lotem Joseph; Tsvetkov Peter; Reiss Veronica; Sachs Leo; Shaul Yosef  
 CORPORATE SOURCE: Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel.  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2003 Dec 9) 100 (25) 15065-70.  
 Electronic Publication: 2003-11-21.  
 Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200401  
 ENTRY DATE: Entered STN: 20031216  
 Last Updated on STN: 20040124  
 Entered Medline: 20040123

AB Proteasomal degradation of **p53** is mediated by two alternative pathways that are either dependent or independent of both Mdm2 and ubiquitin. The ubiquitin-independent pathway is regulated by NAD(P)H:quinone oxidoreductase 1 (NQO1) that **stabilizes p53**. The NQO1 inhibitor dicoumarol induces ubiquitin-independent **p53** degradation. We now show that, like dicoumarol, several other coumarin and flavone inhibitors of NQO1 activity, which compete with NAD(P)H for binding to NQO1, induced ubiquitin-independent **p53** degradation and inhibited wild-type **p53**-mediated apoptosis. Although wild-type **p53** and several **p53** **mutants** were sensitive to dicoumarol-induced degradation, the most frequent "hot-spot" **p53** **mutants** in human cancer, **R175H**, **R248H**, and **R273H**, were resistant to dicoumarol-induced degradation, but

remained sensitive to Mdm2-ubiquitin-mediated degradation. The two alternative pathways for **p53** degradation thus have different **p53** structural requirements. Further mutational analysis showed that arginines at positions 175 and 248 were essential for dicoumarol-induced **p53** degradation. NQO1 bound to wild-type **p53** and dicoumarol, which induced a conformational change in NQO1, inhibited this binding. Compared with wild-type **p53**, the hot-spot **p53** mutants showed increased binding to NQO1, which can explain their resistance to dicoumarol-induced degradation. NQO1 thus has an important role in **stabilizing** hot-spot **p53** mutant proteins in human cancer.

L12 ANSWER 7 OF 24 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 2003089069 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 12600206  
 TITLE: Structure, function, and aggregation of the zinc-free form of the **p53** DNA binding domain.  
 AUTHOR: Butler James S; Loh Stewart N  
 CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, State University of New York Upstate Medical University, 750 East Adams Street, Syracuse, New York 13210, USA.  
 SOURCE: Biochemistry, (2003 Mar 4) 42 (8) 2396-403.  
 Journal code: 0370623. ISSN: 0006-2960.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200305  
 ENTRY DATE: Entered STN: 20030226  
 Last Updated on STN: 20030529  
 Entered Medline: 20030528

AB The **p53** DNA binding domain (DBD) contains a single bound zinc ion that is essential for activity. Zinc remains bound to wild-type DBD at temperatures below 30 degrees C; however, it rapidly dissociates at physiological temperature. The resulting zinc-free protein (apoDBD) is folded and **stable**. NMR spectra reveal that the DNA binding surface is altered in the absence of Zn(2+). Fluorescence anisotropy studies show that Zn(2+) removal abolishes site-specific DNA binding activity, although full nonspecific DNA binding affinity is retained. Surprisingly, the majority of tumorigenic mutations that destabilize DBD do not appreciably destabilize apoDBD. The **R175H** mutation instead substantially accelerates the rate of Zn(2+) loss. A considerable fraction of cellular **p53** may therefore exist in the folded zinc-free form, especially when tumorigenic mutations are present. ApoDBD appears to promote aggregation of zinc-bound DBD via a nucleation-growth process. These data provide an explanation for the dominant negative phenotype exhibited by many mutations. Through a combination of induced **p53** aggregation and diminished site-specific DNA binding activity, Zn(2+) loss may represent a significant inactivation pathway for **p53** in the cell.

L12 ANSWER 8 OF 24 MEDLINE on STN DUPLICATE 6  
 ACCESSION NUMBER: 2003468465 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14529628  
 TITLE: Conversion of wild-type **p53** core domain into a conformation that mimics a hot-spot mutant.

AUTHOR: Ishimaru Daniella; Maia Lenize F; Maiolino Larissa M;  
 Quesado Pablo A; Lopez Priscila C M; Almeida Fabio C L;  
 Valente Ana Paula; Silva Jerson L  
 CORPORATE SOURCE: Departamento de Bioquimica Medica, Centro Nacional de  
 Ressonancia Magnetica Nuclear de Macromoleculas, Instituto  
 de Ciencias Biomedicas, Universidade Federal do Rio de  
 Janeiro, Rio de Janeiro, RJ 21941-590, Brazil.  
 SOURCE: Journal of molecular biology, (2003 Oct 17) 333 (2) 443-51.  
 Journal code: 2985088R. ISSN: 0022-2836.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200311  
 ENTRY DATE: Entered STN: 20031008  
 Last Updated on STN: 20031111  
 Entered Medline: 20031110

AB The wild-type **p53** protein can be driven into a conformation corresponding to that adopted by structural mutant forms by heterodimerization with a mutant subunit. To seek partially folded states of the wild-type **p53** core domain (**p53C**) we used high hydrostatic pressure (HP) and subzero temperatures. Aggregation of the protein was observed in parallel with its pressure denaturation at 25 and 37 degrees C. However, when HP experiments were performed at 4 degrees C, the extent of denaturation and aggregation was significantly less pronounced. On the other hand, subzero temperatures under pressure led to cold denaturation and yielded a non-aggregated, alternative conformation of **p53C**. Nuclear magnetic resonance (1H15N-NMR) data showed that the alternative **p53C** conformation resembled that of the hot-spot oncogenic **mutant R248Q**. This alternative state was as susceptible to denaturation and aggregation as the **mutant R248Q** when subjected to HP at 25 degrees C. Together these data demonstrate that wild-type **p53C** adopts an alternative conformation with a mutant-like **stability**, consistent with the dominant-negative effect caused by many mutants. This alternative conformation is likely related to inactive forms that appear *in vivo*, usually driven by interaction with mutant proteins. Therefore, it can be a valuable target in the search for ways to interfere with protein misfolding and hence to prevent tumor development.

L12 ANSWER 9 OF 24 MEDLINE on STN DUPLICATE 7  
 ACCESSION NUMBER: 2003509914 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 14587098  
 TITLE: Elevated levels of prostate-specific antigen (PSA) in prostate cancer cells expressing mutant **p53** is associated with tumor metastasis.  
 AUTHOR: Downing Sean; Bumak Clare; Nixdorf Sheri; Ow Kim; Russell Pamela; Jackson Paul  
 CORPORATE SOURCE: Oncology Research Centre, Prince of Wales Hospital, Randwick, NSW, Australia.  
 SOURCE: Molecular carcinogenesis, (2003 Nov) 38 (3) 130-40.  
 Journal code: 8811105. ISSN: 0899-1987.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200312

ENTRY DATE:                   Entered STN: 20031031  
                                  Last Updated on STN: 20031219  
                                  Entered Medline: 20031212

AB    The underlying basis for rising levels of prostate-specific antigen (PSA) in prostate cancer is not fully understood, but attention has turned to the possibility that loss of normal p53 function might be directly involved. We have investigated the relationship between p53 function and PSA expression using in vitro and in vivo approaches. Three prostate cancer-derived p53 mutants (F134L, M237L, R273H) were introduced into LNCaP prostate cancer cells and stable transfectants established. Expression of mutant p53 was demonstrated by Western blot analysis, inactivation of wtp53 function, and a loss of p53-dependent responses to DNA damage induced by UV-irradiation and cisplatin. Levels of PSA mRNA and secreted protein were determined by RT-PCR and Western blotting, respectively. Serine protease activity was assessed using an esterase assay. In vivo effects of mutant p53 expression were examined after orthotopic implantation into prostates of nude mice. Expression of all p53 mutants was associated with elevated PSA mRNA and secreted PSA protein. In a representative line, mutant p53 was also associated with increased PSA protease-like activity compared with a control line expressing wildtype p53. Overall PSA levels, and PSA levels in serum from mice bearing tumors derived from cells expressing mutant p53, were increased compared with levels in mice bearing tumors derived from control cells. In addition, the tumors derived from cells with mutant p53 had increased vascularization and induced lymph node metastases. These data provide in vitro and in vivo support for the notion that p53 mutations directly contribute to increased levels of serum PSA, and are associated with more aggressive tumors.

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L12 ANSWER 10 OF 24           MEDLINE on STN                           DUPLICATE 8  
 ACCESSION NUMBER:    2002210482           MEDLINE  
 DOCUMENT NUMBER:    PubMed ID: 11948395  
 TITLE:                   Characterization of the p53-rescue drug CP-31398  
                           in vitro and in living cells.  
 AUTHOR:                Rippin Thomas M; Bykov Vladimir J N; Freund Stefan M V;  
                           Selivanova Galina; Wiman Klas G; Fersht Alan R  
 CORPORATE SOURCE:    Cambridge University Chemical Laboratory and Cambridge  
                           Center for Protein Engineering, MRC Centre, Hills Road,  
                           Cambridge CB2 2QH, UK.  
 SOURCE:                Oncogene, (2002 Mar 28) 21 (14) 2119-29.  
                           Journal code: 8711562. ISSN: 0950-9232.  
 PUB. COUNTRY:        England: United Kingdom  
 DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE:            English  
 FILE SEGMENT:       Priority Journals  
 ENTRY MONTH:        200204  
 ENTRY DATE:         Entered STN: 20020412  
                          Last Updated on STN: 20020501  
                          Entered Medline: 20020430

AB    The Pfizer compound CP-31398 has been reported to stabilize the core domain of the tumour suppressor p53 in vitro and be an effective anti-cancer drug by virtue of rescuing destabilized mutants of p53. We did not detect any interaction between the p53

core domain and CP-31398 in vitro by a wide range of quantitative biophysical techniques over a wide range of conditions. CP-31398 did not stabilize p53 in our experiments. However, we found that CP-31398 intercalated with DNA and also altered and destabilized the DNA-p53 core domain complex. We analysed by NMR TROSY the interaction of the domain with a DNA oligomer and identified the changes in the complex on the binding of CP-31398. CP-31398 also decreased sequence-specific DNA binding of wild-type p53 and His-273 mutant p53. CP-31398 had a non-specific toxic effect independent of mutant p53 expression in several cell lines carrying Tet-regulated mutant p53. CP-31398 caused a small increase in MDM-2 expression and a more pronounced p53 -independent increase in Bax expression. CP-31398 did, however, induce the PAb1620 epitope (characteristic of native p53) in cells expressing His-175 mutant p53. This was prevented by cycloheximide, suggesting that any stabilizing action of CP-31398 would have to be on newly synthesized p53. One of the unstable mutants that was reported to have been rescued by CP-31398, R249S, does not bind DNA when folded at lower temperatures.

L12 ANSWER 11 OF 24 MEDLINE on STN DUPLICATE 9  
 ACCESSION NUMBER: 2002175455 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11782540  
 TITLE: A peptide that binds and stabilizes p53  
 core domain: chaperone strategy for rescue of oncogenic mutants.  
 AUTHOR: Friedler Assaf; Hansson Lars O; Veprintsev Dmitry B; Freund Stefan M V; Rippin Thomas M; Nikolova Penka V; Proctor Mark R; Rudiger Stefan; Fersht Alan R  
 CORPORATE SOURCE: Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, Medical Research Council Centre, Hills Road, Cambridge CB2 2QH, United Kingdom.  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2002 Jan 22) 99 (2) 937-42.  
 Electronic Publication: 2002-01-08.  
 Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200204  
 ENTRY DATE: Entered STN: 20020324  
 Last Updated on STN: 20030105  
 Entered Medline: 20020429  
 AB Conformationally compromised oncogenic mutants of the tumor suppressor protein p53 can, in principle, be rescued by small molecules that bind the native, but not the denatured state. We describe a strategy for the rational search for such molecules. A nine-residue peptide, CDB3, which was derived from a p53 binding protein, binds to p53 core domain and stabilizes it in vitro. NMR studies showed that CDB3 bound to p53 at the edge of the DNA binding site, partly overlapping it. The fluorescein-labeled peptide, FL-CDB3, binds wild-type p53 core domain with a dissociation constant of 0.5 microM, and raises the apparent melting temperatures of wild-type and a representative oncogenic mutant, R249S core domain.

gadd45 DNA competes with CDB3 and displaces it from its binding site. But this competition does not preclude CDB3 from being a lead compound. CDB3 may act as a "chaperone" that maintains existing or newly synthesized destabilized **p53** mutants in a native conformation and then allows transfer to specific DNA, which binds more tightly. Indeed, CDB3 restored specific DNA binding activity to a highly destabilized **mutant I195T** to close to that of wild-type level.

L12 ANSWER 12 OF 24 MEDLINE on STN DUPLICATE 10  
 ACCESSION NUMBER: 2001352168 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11416144  
 TITLE: ZBP-89 promotes growth arrest through **stabilization** of **p53**.  
 AUTHOR: Bai L; Merchant J L  
 CORPORATE SOURCE: Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA.  
 CONTRACT NUMBER: 5P30 CA46592-13 (NCI)  
 DK 55732 (NIDDK)  
 SOURCE: Molecular and cellular biology, (2001 Jul) 21 (14) 4670-83.  
 Journal code: 8109087. ISSN: 0270-7306.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200107  
 ENTRY DATE: Entered STN: 20010730  
 Last Updated on STN: 20010730  
 Entered Medline: 20010726

AB Transcription factor **p53** can induce growth arrest and/or apoptosis in cells through activation or repression of downstream target genes. Recently, we reported that ZBP-89 cooperates with histone acetyltransferase coactivator p300 in the regulation of p21(waf1), a cyclin-dependent kinase inhibitor whose associated gene is a target gene of **p53**. Therefore, we examined whether ZBP-89 might also inhibit cell growth by activating **p53**. In the present study, we demonstrate that elevated levels of ZBP-89 induce growth arrest and apoptosis in human gastrointestinal cell lines. The ZBP-89 protein accumulated within 4 h, and the **p53** protein accumulated within 16 h, of serum starvation without changes in p14ARF levels, demonstrating a physiological increase in the cellular levels of these two proteins. Overexpression of ZBP-89 **stabilized** the **p53** protein and enhanced its transcriptional activity through direct protein-protein interactions. The DNA binding and C-terminal domains of **p53** and the zinc finger domain of ZBP-89 mediated the interaction. A point **mutation** in the **p53** DNA binding domain, **R273H**, greatly reduced ZBP-89-mediated **stabilization** but not their physical interaction. Furthermore, ZBP-89 formed a complex with **p53** and MDM2 and therefore did not prevent the MDM2-**p53** interaction. However, heterokaryon assays demonstrated that ZBP-89 retained **p53** in the nucleus. Collectively, these data indicate that ZBP-89 regulates cell proliferation in part through its ability to directly bind the **p53** protein and retard its nuclear export. Our findings further our understanding of how ZBP-89 modulates cell proliferation and reveals a novel mechanism by which the **p53** protein is **stabilized**.

L12 ANSWER 13 OF 24 MEDLINE on STN DUPLICATE 11  
 ACCESSION NUMBER: 2001214517 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11172034  
 TITLE: **p53** associates with and targets Delta Np63 into a protein degradation pathway.  
 AUTHOR: Ratovitski E A; Paturajan M; Hibi K; Trink B; Yamaguchi K; Sidransky D  
 CORPORATE SOURCE: Department of Otolaryngology-Head and Neck Surgery, Division of Head and Neck Cancer Research, The Johns Hopkins University School of Medicine, Baltimore, MD 21205-2196, USA.. erat@welch.jhu.edu  
 CONTRACT NUMBER: CA-58184-01 (NCI)  
 R01-AI-47224-01 (NIAID)  
 R01-DE-012588-01 (NIDCR)  
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2001 Feb 13) 98 (4) 1817-22. Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200104  
 ENTRY DATE: Entered STN: 20010425  
 Last Updated on STN: 20010425  
 Entered Medline: 20010419  
 AB A human **p53** homologue, p63 (p40/p51/p73L/CUSP) that maps to the chromosomal region 3q27-29 was found to produce a variety of transcripts that encode DNA-binding proteins with and without a trans-activation domain (TA- or Delta N-, respectively). The p63 gene locus was found to be amplified in squamous cell carcinoma, and overexpression of Delta Np63 (p40) led to increased growth of transformed cells in vitro and in vivo. Moreover, p63-null mice displayed abnormal epithelial development and germ-line human mutations were found to cause ectodermal dysplasia. We now demonstrate that certain p63 isotypes form complexes with **p53**.  
 . **p53** mutations R175H or R248W abolish the association of **p53** with p63, whereas V143A or R273H has no effect. Deletion studies suggest that the DNA-binding domains of both **p53** and p63 mediate the association. Overexpression of wild type but not mutant (R175H) **p53** results in the caspase-dependent degradation of certain Delta Np63 proteins (p40 and Delta Np63 alpha). The association between **p53** and Delta Np63 supports a previously unrecognized role for **p53** in regulation of Delta Np63 stability. The ability of **p53** to mediate Delta Np63 degradation may balance the capacity of Delta Np63 to accelerate tumorigenesis or to induce epithelial proliferation.

L12 ANSWER 14 OF 24 MEDLINE on STN DUPLICATE 12  
 ACCESSION NUMBER: 2001244234 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11314010  
 TITLE: p73 is transcriptionally regulated by DNA damage, **p53**, and p73.  
 AUTHOR: Chen X; Zheng Y; Zhu J; Jiang J; Wang J  
 CORPORATE SOURCE: Institute of Molecular Medicine and Genetics, Medical College of Georgia, Augusta, GA 30912, USA.  
 CONTRACT NUMBER: CA76069 (NCI)  
 R01 CA81237 (NCI)

SOURCE: Oncogene, (2001 Feb 8) 20 (6) 769-74.  
 Journal code: 8711562. ISSN: 0950-9232.

PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200105

ENTRY DATE: Entered STN: 20010517  
 Last Updated on STN: 20010517  
 Entered Medline: 20010510

AB p73 is a member of the p53 family. Recent studies have shown that DNA damage can stabilize p73 protein and enhance p73-mediated apoptosis in a c-Abl dependent manner. To determine what regulates p73 transcriptionally, we analysed the expression of p73 in several cell lines following genotoxic stresses. We found that p73 is induced in certain cell lines when treated with therapeutic DNA damaging agents. We also found that p53 and p73, but not mutant p53(R249S) and p73beta292, directly induce the expression of the p73 gene. In addition, we found one potential p53-binding site in the promoter of the p73 gene. This binding site is responsive to p53, p73, and DNA damage. Taken together, these data suggest that p73 is transcriptionally regulated by DNA damage and p53, and is autoregulated.

L12 ANSWER 15 OF 24 MEDLINE on STN DUPLICATE 13  
 ACCESSION NUMBER: 2001377498 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 11435891  
 TITLE: Various forms of mutant p53 confer sensitivity to cisplatin and doxorubicin in bladder cancer cells.  
 AUTHOR: Chang F L; Lai M D  
 CORPORATE SOURCE: Department of Biochemistry, College of Medicine, National Cheng Kung University, Tainan, Taiwan, Republic of China.  
 SOURCE: Journal of urology, (2001 Jul) 166 (1) 304-10.  
 Journal code: 0376374. ISSN: 0022-5347.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200108  
 ENTRY DATE: Entered STN: 20010813  
 Last Updated on STN: 20010813  
 Entered Medline: 20010809

AB PURPOSES: The nature of p53 mutation has been reported to affect cellular responses to chemotherapy. We characterized the impact of p53 mutations on drug resistance in bladder cancer cells. METHODS AND METHODS: Various human p53 mutants (V143A, V173L, H179Q, N247I and R273H) were introduced to the TCC-SUP bladder carcinoma cell line to establish stable transfectants. The expression of mutant p53 was demonstrated by reverse transcriptase-polymerase chain reaction and immunocytochemical analysis. The sensitivity to cisplatin and doxorubicin in these transfectants was determined by trypan blue exclusion. Cell death mediated by cisplatin and doxorubicin was characterized by terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling analysis, Hoechst 33258 staining and annexin-V binding assay. RESULTS: The expression of all forms of mutant p53 protein except p53His273

enhanced sensitivity to cisplatin and doxorubicin. The chemosensitivity of p53His273 transfectants is similar to that of parental TCC-SUP and control transfectants. Cisplatin induced cell death undergoes apoptosis, as demonstrated by Hoechst staining, annexin-V assay and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling, respectively. In contrast, doxorubicin induced cell death probably occurs through a nonapoptotic pathway. CONCLUSIONS: These results indicated that the nature of p53 mutations may affect the cellular response to anticancer drugs and many forms of mutant p53 protein may enhance chemosensitivity through apoptotic or nonapoptotic pathways in bladder cancer cells.

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STN DUPLICATE 14

ACCESSION NUMBER: 2000:166344 BIOSIS  
DOCUMENT NUMBER: PREV200000166344  
TITLE: Quantitative analysis of residual folding and DNA binding in mutant p53 core domain: Definition of mutant states for rescue in cancer therapy.  
AUTHOR(S): Bullock, Alex N.; Henckel, Julia; Fersht, Alan R. [Reprint author]  
CORPORATE SOURCE: Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, Medical Research Council Centre, Hills Road, Cambridge, CB2 2QH, UK  
SOURCE: Oncogene, (March 2, 2000) Vol. 19, No. 10, pp. 1245-1256. print.  
CODEN: ONCNES. ISSN: 0950-9232.  
DOCUMENT TYPE: Article  
LANGUAGE: English  
ENTRY DATE: Entered STN: 3 May 2000  
Last Updated on STN: 4 Jan 2002

AB The tumour suppressor p53 is mutated in half of all human cancers, most frequently with missense substitutions in its core domain. We present a new assessment of the mutation database based on quantitative folding and DNA-binding studies of the isolated core domain. Our data identify five distinct mutant classes that correlate with four well-defined regions of the core domain structure. On extrapolation to 37degreeC the wild-type protein has a stability of 3.0 kcal/mol. This also emerges as an oncogenic threshold: all beta-sandwich mutants destabilized by this amount (50% denatured) are expected to promote cancer. Other weakly destabilizing mutations are restricted to loop 3 in the DNA-binding region. Drugs that stabilize mutant p53 folding have the potential to reactivate apoptotic signalling pathways in tumour cells either by transactivation-dependent or independent pathways. Using an affinity ligand as a proof of principle we have recovered the thermodynamic stability of the hotspot G245S. With reference states for the five mutant classes as a guide, future therapeutic strategies may similarly stabilize partially structured or binding states of mutant p53 that restore limited p53 pathways to tumour suppression.

L12 ANSWER 17 OF 24 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on  
STN  
ACCESSION NUMBER: 2000:478769 BIOSIS  
DOCUMENT NUMBER: PREV200000478769  
TITLE: Stability studies of p53 tumour

AUTHOR(S): suppressor mutants.  
 Nikolova, Penka V. [Reprint author]; Wong, Kam-Bo [Reprint author]; Dedecker, Brian [Reprint author]; Henckel, Julia [Reprint author]; Fersht, Alan R. [Reprint author]  
 CORPORATE SOURCE: MRC Centre, Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, Hills Road, Cambridge, CB2 2QH, UK  
 SOURCE: Journal of Biomolecular Structure and Dynamics, (June, 2000) Vol. 17, No. 6, pp. 1149-1150. print.  
 Meeting Info.: Conference on DNA Structure and Interactions: Their Biological Roles and Implications in Biomedicine and Biotechnologies. Brno, Czech Republic. July 19-23, 2000.  
 CODEN: JBSDD6. ISSN: 0739-1102.  
 DOCUMENT TYPE: Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LANGUAGE: English  
 ENTRY DATE: Entered STN: 8 Nov 2000  
 Last Updated on STN: 10 Jan 2002

L12 ANSWER 18 OF 24 MEDLINE on STN DUPLICATE 15  
 ACCESSION NUMBER: 2000120801 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10654936  
 TITLE: Mechanism of rescue of common **p53** cancer mutations by second-site suppressor mutations.  
 AUTHOR: Nikolova P V; Wong K B; DeDecker B; Henckel J; Fersht A R  
 CORPORATE SOURCE: Cambridge University Chemical Laboratory and Cambridge Centre for Protein Engineering, MRC Centre, Hills Road, Cambridge CB2 2QH, UK.  
 SOURCE: EMBO journal, (2000 Feb 1) 19 (3) 370-8.  
 Journal code: 8208664. ISSN: 0261-4189.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200003  
 ENTRY DATE: Entered STN: 20000327  
 Last Updated on STN: 20000327  
 Entered Medline: 20000310

AB The core domain of **p53** is extremely susceptible to mutations that lead to loss of function. We analysed the **stability** and DNA-binding activity of such mutants to understand the mechanism of second-site suppressor mutations. Double-mutant cycles show that N239Y and N268D act as 'global **stability**' suppressors by increasing the **stability** of the cancer mutants **G245S** and **V143A**-the free energy changes are additive. Conversely, the suppressor H168R is specific for the **R249S mutation**: despite destabilizing wild type, H168R has virtually no effect on the **stability** of **R249S**, but restores its binding affinity for the gadd45 promoter. NMR structural comparisons of R249S/H168R and R249S/T123A/H168R with wild type and R249S show that H168R reverts some of the structural changes induced by R249S. These results have implications for possible drug therapy to restore the function of tumorigenic mutants of **p53**: the function of mutants such as **V143A** and **G245S** is theoretically possible to restore by small molecules that simply bind to and hence **stabilize** the native

structure, whereas **R249S** requires alteration of its **mutant** native structure.

L12 ANSWER 19 OF 24 MEDLINE on STN DUPLICATE 16  
 ACCESSION NUMBER: 1999243189 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 10226602  
 TITLE: Modulation of wild-type **p53** activity by **mutant p53 R273H** depends on the **p53** responsive element (p53RE). A comparative study between the p53REs of the MDM2, WAF1/Cip1 and Bax genes in the lung cancer environment. WAF1/Cip1 = WAF1/Cip1.  
 AUTHOR: Zacharatos P V; Gorgoulis V G; Kotsinas A; Manolis E N; Liloglou T; Rassidakis A N; Kanavaros P; Field J D; Halazonetis T; Kittas C  
 CORPORATE SOURCE: Department of Histology and Embryology, School of Medicine, University of Athens, Greece.  
 SOURCE: Anticancer research, (1999 Jan-Feb) 19 (1A) 579-87.  
 Journal code: 8102988. ISSN: 0250-7005.  
 PUB. COUNTRY: Greece  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199905  
 ENTRY DATE: Entered STN: 19990601  
 Last Updated on STN: 19990601  
 Entered Medline: 19990520  
 AB Wild-type (wt) **p53** is a tumor-suppressor protein which acts via transcriptional and transcriptional-independent mechanisms. The transcriptional function of **p53** is mediated by specific responsive elements (REs). The MDM2, WAF1/Cip1 and Bax genes possess p53REs and their activation by wt **p53** induces cell cycle progression, arrest and programmed cell death (apoptosis), respectively. Mutations of the **p53** gene are detected in more than 50% of the human malignant tumors. **p53** mutants seem to have a more stable conformation and are suggested to exert dominant-negative inhibition of wt **p53** in cells containing both wt and mutant (mt) alleles. However, recent studies show that certain mt **p53** proteins posses a "gain of function" phenotype. In the present study, we examined the effects of the second most frequent **p53** mutant **R273H** on the p53REs of the MDM2, WAF1/Cip1 and Bax genes in the H1299 non-small cell lung carcinoma cell line. Although mt **p53** R273H alone was unable to bind and transactivate the corresponding p53REs, it enhanced the MDM2-p53RE mediated gene transcription of wt **p53** (positive-dominant effect) and prevented the wt **p53** transactivation of the p53REs of WAF1/Cip1 and Bax genes (negative-dominant effect). Our data suggest that in the appropriate environment, differential transcription of critical **p53** target genes by certain **p53** mutant proteins may illustrate another mechanism implicated in tumor development.

L12 ANSWER 20 OF 24 MEDLINE on STN DUPLICATE 17  
 ACCESSION NUMBER: 1998216785 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9557707  
 TITLE: Adenovirus type 12-induced fragility of the human RNU2 locus requires **p53** function.  
 AUTHOR: Li Z; Yu A; Weiner A M

CORPORATE SOURCE: Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut 06520-8114, USA.

CONTRACT NUMBER: GM31073 (NIGMS)  
GM41624 (NIGMS)

SOURCE: Journal of virology, (1998 May) 72 (5) 4183-91.

Journal code: 0113724. ISSN: 0022-538X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199805

ENTRY DATE: Entered STN: 19980529

Last Updated on STN: 19990129

Entered Medline: 19980520

AB Adenovirus type 12 (Ad12) infection of human cells induces four chromosomal fragile sites corresponding to the U1 small nuclear RNA (snRNA) genes (the RNU1 locus), the U2 snRNA genes (RNU2), the U1 snRNA pseudogenes (PSU1), and the 5S rRNA genes (RN5S). Ad12-induced fragility of the RNU2 locus requires U2 snRNA transcriptional regulatory elements and viral early functions but not viral replication or integration, or chromosomal sequences flanking the RNU2 locus. We now show that Ad12 cannot induce the RNU1, RNU2, or PSU1 fragile sites in Saos-2 cells lacking the p53 and retinoblastoma (Rb) proteins but that viral induction of fragility is rescued in these cells when the expression of wild-type p53 or selected hot-spot mutants (i.e., V143A, R175H, R248W, and R273H) is restored by transient expression or stable retroviral transduction. We also observed weak constitutive fragility of the RNU1 and RNU2 loci in cells belonging to xeroderma pigmentosum complementation groups B and D (XPB and XPD) which are partially defective in the ERCC2 (XPD) and ERCC3 (XPB) helicase activities shared between the reparaosome and the RNA polymerase H basal transcription factor TFIIH. We propose a model for Ad12-induced chromosome fragility in which interaction of p53 with the Ad12 E1B 55-kDa transforming protein (and possibly E4orf6) induces a p53 gain of function which ultimately perturbs the RNA polymerase II basal transcription apparatus. The p53 gain of function could interfere with chromatin condensation either by blocking mitotic shutdown of U1 and U2 snRNA transcription or by phenocopying global or local DNA damage. Specific fragilization of the RNU1, RNU2, and PSU1 loci could reflect the unusually high local concentration of strong transcription units or the specialized nature of the U1 and U2 snRNA transcription apparatus.

L12 ANSWER 21 OF 24 MEDLINE on STN DUPLICATE 18  
ACCESSION NUMBER: 1998190068 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 9524109  
TITLE: Genetic selection of intragenic suppressor mutations that reverse the effect of common p53 cancer mutations.  
AUTHOR: Brachmann R K; Yu K; Eby Y; Pavletich N P; Boeke J D  
CORPORATE SOURCE: Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.  
CONTRACT NUMBER: CA 16519 (NCI)  
SOURCE: EMBO journal, (1998 Apr 1) 17 (7) 1847-59.  
Journal code: 8208664. ISSN: 0261-4189.

PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199806  
 ENTRY DATE: Entered STN: 19980611  
                   Last Updated on STN: 19980611  
                   Entered Medline: 19980601

AB Several lines of evidence suggest that the presence of the wild-type tumor suppressor gene **p53** in human cancers correlates well with successful anti-cancer therapy. Restoration of wild-type **p53** function to cancer cells that have lost it might therefore improve treatment outcomes. Using a systematic yeast genetic approach, we selected second-site suppressor mutations that can overcome the deleterious effects of common **p53** cancer mutations in human cells. We identified several suppressor mutations for the **V143A**, **G245S** and **R249S** cancer mutations. The beneficial effects of these suppressor mutations were demonstrated using mammalian reporter gene and apoptosis assays. Further experiments showed that these suppressor mutations could override additional **p53** cancer mutations. The mechanisms of such suppressor mutations can be elucidated by structural studies, ultimately leading to a framework for the discovery of small molecules able to stabilize **p53** mutants.

L12 ANSWER 22 OF 24 MEDLINE on STN DUPLICATE 19  
 ACCESSION NUMBER: 1998070752 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 9405613  
 TITLE: Thermodynamic stability of wild-type and mutant  
       **p53** core domain.  
 AUTHOR: Bullock A N; Henckel J; DeDecker B S; Johnson C M; Nikolova  
       P V; Proctor M R; Lane D P; Fersht A R  
 CORPORATE SOURCE: Cambridge University Chemical Laboratory and Cambridge  
       Centre for Protein Engineering, Medical Research Council  
       Centre, Hills Road, Cambridge CB2 2QH, United Kingdom.  
 SOURCE: Proceedings of the National Academy of Sciences of the  
       United States of America, (1997 Dec 23) 94 (26) 14338-42.  
       Journal code: 7505876. ISSN: 0027-8424.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199802  
 ENTRY DATE: Entered STN: 19980217  
                   Last Updated on STN: 19980217  
                   Entered Medline: 19980202

AB Some 50% of human cancers are associated with mutations in the core domain of the tumor suppressor **p53**. Many mutations are thought just to destabilize the protein. To assess this and the possibility of rescue, we have set up a system to analyze the stability of the core domain and its mutants. The use of differential scanning calorimetry or spectroscopy to measure its melting temperature leads to irreversible denaturation and aggregation and so is useful as only a qualitative guide to stability. There are excellent two-state denaturation curves on the addition of urea that may be analyzed quantitatively. One Zn<sup>2+</sup> ion remains tightly bound in the holo-form of **p53** throughout the

denaturation curve. The **stability** of wild type is 6.0 kcal (1 kcal = 4.18 kJ)/mol at 25 degrees C and 9.8 kcal/mol at 10 degrees C. The oncogenic mutants **R175H**, **C242S**, **R248Q**, **R249S**, and **R273H** are destabilized by 3.0, 2.9, 1.9, 1.9, and 0.4 kcal/mol, respectively. Under certain denaturing conditions, the wild-type domain forms an aggregate that is relatively highly fluorescent at 340 nm on excitation at 280 nm. The destabilized mutants give this fluorescence under milder denaturation conditions.

L12 ANSWER 23 OF 24 CANCERLIT on STN  
 ACCESSION NUMBER: 97618953 CANCERLIT  
 DOCUMENT NUMBER: 97618953  
 TITLE: Doxorubicin induces G2/M arrest and apoptosis in the p53 mutant cell line HT-29 (Meeting abstract).  
 AUTHOR: Giacoma M; Brown T; Giedlin M; Yamamoto R  
 CORPORATE SOURCE: CHIRON Corp. Dept of Pharmacology, BioPharmaceutical Evaluation, Emeryville, CA 94608.  
 SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A131.  
 ISSN: 0197-016X.  
 DOCUMENT TYPE: (MEETING ABSTRACTS)  
 LANGUAGE: English  
 FILE SEGMENT: Institute for Cell and Developmental Biology  
 ENTRY MONTH: 199709  
 ENTRY DATE: Entered STN: 19980417  
 Last Updated on STN: 19980417

AB Normal cells are thought to acquire a cancerous phenotype through a process involving multiple genetic changes. The nuclear phosphoprotein p53 is a tumor suppressor that functions to maintain genomic **stability** in cells by inducing growth arrest or apoptosis. Cells with **mutations** that result in altered or non-functional p53 protein are highly selected for during cancer progression. Most if not all chemotherapeutics kill tumor cells by triggering apoptosis. To better understand the mechanisms behind cancer chemotherapeutics in a p53 mutant background a human colon adenocarcinoma cell line HT-29 (**R273H**) was used as a model system. Doxorubicin induced the gene expression of p21waf1/cip1 a cyclin-dependent kinase inhibitor within 3 hours of exposure. Flow cytometry analysis of propidium iodide and FITC-dUTP stained cells showed growth arrest and apoptosis at G2/M. As a biochemical indicator of apoptosis the fluorescent substrate DEVD-AFC was used to monitor the appearance of apoptosis-associated cysteine protease activity in doxorubicin-treated cells. Enzyme activity in HT29 cells was detected at 48 hrs and in HCT116 cells at 24 hrs. The relative potencies of several clinically relevant chemotherapeutics were rank ordered by this enzyme assay: (Doxorubicin=Camptothecin greater than Paclitaxel=Etoposide). Insights into the cell cycle checkpoints and apoptosis in normal vs cancer cells provides a useful framework for identifying new agents for antineoplastic therapy and alternative uses for conventional chemotherapeutics.

L12 ANSWER 24 OF 24 CANCERLIT on STN  
 ACCESSION NUMBER: 96601077 CANCERLIT  
 DOCUMENT NUMBER: 96601077  
 TITLE: Use of temperature-sensitive (TS) mutants of the v-Rel oncoprotein to study apoptosis in chicken spleen cells (Meeting abstract).

AUTHOR: White D; Gilmore T  
CORPORATE SOURCE: Biology Department, Boston University, Boston, MA 02215.  
SOURCE: J Cell Biochem, (1995) Suppl 19A 64.

ISSN: 0730-2312.

DOCUMENT TYPE: (MEETING ABSTRACTS)

LANGUAGE: English

FILE SEGMENT: Institute for Cell and Developmental Biology

ENTRY MONTH: 199603

ENTRY DATE: Entered STN: 19970509

Last Updated on STN: 19970509

AB The v-Rel nuclear oncprotein is a transcription factor encoded by the avian Rev-T retrovirus that can transform and immortalize chicken spleen cells in vitro. We have constructed two ts v-Rel mutants (v-R273H and v-G37E) that are ts for transformation and DNA binding. When ts v-Rel-transformed chicken spleen cells are shifted to the nonpermissive temperature, the cells rapidly undergo apoptosis, as characterized by condensed chromatin and the formation of 'DNA ladders.' Many proteins, including v-Rel, Bcl-2, c-Myc, Rb and p53, are quite stable in these cells while undergoing apoptosis. However, the v-Rel-associated protein p40 (I kappa B-alpha) is specifically degraded when ts v-Rel-transformed cells are shifted to the nonpermissive temperature. In cells transformed by ts v-Rel mutant v-R273H, p40 is completely degraded, similar to what is observed in other cells in which Rel complexes are induced to enter the nucleus. In cells transformed by ts v-Rel mutant v-G37E, p40 is cleaved to an intermediate form, which is found in a detergent-insoluble fraction and is missing approximately 3 kD from the N terminus. These results suggest that v-Rel stabilizes p40 in transformed cells and that changes in the structure of a Rel/NF-kappa B protein can initiate proteolysis of an associated I kappa B protein. Furthermore, they indicate that v-Rel blocks a normal pathway of programmed cell death as part of its transforming and immortalizing process. We are currently attempting to understand the molecular basis for v-Rel-mediated inhibition of apoptosis.

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